HHS Public Access

Author manuscript

J Allergy Clin Immunol Pract. Author manuscript; available in PMC 2016 November 01.

Published in final edited form as:

J Allergy Clin Immunol Pract. 2015 ; 3(6): 934–940.e3. doi:10.1016/j.jaip.2015.06.018.

Symptom-based Clustering In Chronic Rhinosinusitis Relates To History of Aspirin Sensitivity and Post-surgical Outcomes

Rohit Divekar, MBBS, PhD[1,*], **Neil Patel, MD**[2], **Jay Jin, MD**[1], **John Hagan, MD**[1], **Matthew Rank, MD**[3], **Devyani Lal, MD**[4], **Hirohito Kita, MD**[1], and **Erin O'Brien, MD**[2]

[1]Division of Allergic Diseases, Department of Medicine, Mayo Clinic, Rochester, MN USA

[2]Department of Otorhinolaryngology, Mayo Clinic, Rochester, MN USA

[3]Division of Allergy, Asthma, and Clinical Immunology, Mayo Clinic, Scottsdale, AZ USA

[4]Department of Otolaryngology, Mayo Clinic, Phoenix, AZ USA

Abstract

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 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 pre-operative 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 ninety-seven surgical CRS patients. Symptom based clusters were derived based on presurgical SNOT-22 scores using unsupervised analysis and network graphs. Comparison between clusters was performed for clinical and demographic parameters, post-surgical symptom scores, and presence or absence of a history of aspirin sensitivity.

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

Conclusion—Symptom based clusters in chronic rhinosinusitis reveal a distinct grouping of symptom burden which may relate to aspirin sensitivity and treatment outcomes.

[*]Corresponding author: Division of Allergic Diseases, 200 First Street SW, Rochester, MN 55905, Phone: 507-284-3783, Fax: 507-284-0902, Divekar.Rohit@mayo.edu.

Part of this study was presented as a poster at the American academy of allergy, asthma and immunology annual meeting in Houston 2015.

Keywords

chronic rhinosinusitis; AERD; aspirin sensitivity; CRS symptoms; SNOT-22

INTRODUCTION

Chronic rhinosinusitis (CRS) is defined as 12 weeks or longer of two 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]. Since the criteria for defining CRS emphasizes symptomatology, measuring and comparing individual or groups of symptoms in CRS is important in assessing disease severity and treatment outcomes. Addition of two questions, impairment of taste/smell and blockage or congestion of the nose, to the well validated CRS SinoNasal Outcome Test (SNOT-20) questionnaire[2] has provided an additional measure of sinonasal disease burden and has also been validated (SNOT-22)[3]. Prior studies have used overall SNOT-22 scores[4, 5], individual scores[6], or *pre-defined* combinations of symptoms[7, 8] and have documented differences in *a priori* defined CRS sub-types (including aspirin sensitivity) in regards to symptom burden[3]. Cluster analysis of symptoms to define such subgroups has recently been attempted,[9, 10] but pre and post therapy differences using unsupervised methods have not been extensively studied. In this paper we obtained pre-operative SNOT-22 scores of patients who underwent endoscopic sinus surgery for CRS, used *unsupervised learning* to model symptom-based patient clusters, and studied the 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 chronic rhinosinusitis seen in Department of Otorhinolaryngology and Division of Allergic diseases at Mayo clinic, Rochester, MN from 2012–14. The study was approved by the institutional review board and clinical data from patient's medical record was 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 greater than 12 weeks[1]. All patients underwent endoscopic sinus surgery (ESS) 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 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 pre-surgical score was 26 days [inter quartile range (IQR) 7 to 41].

Follow up SNOT-22 scores were obtained at an initial postoperative period (median, day 21 IQR 14 to 36) and at a subsequent second visit (median day 97 IQR 58 to 198) after surgery. Additional clinical data was gathered (listed in table 1). Upon further review 11 of 22 patients who reported history of aspirin sensitivity underwent a challenge/desensitization post-surgery in division of allergic diseases.

Clinical and laboratory testing

Vitamin D3 and Serum IgE assessment was done at Mayo Medical laboratory. Eosinophil count prior to surgery as well as 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 (WDC) 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 resultant network to reveal patterns of association. Hierarchical agglomerative clustering was applied to standardized data to reveal cluster membership and boundaries.

Statistical analysis

Chi-Square 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 or Wilcoxon Rank Sums test. P value less than 0.05 was considered as statistically significant. Analysis was performed using JMP software (v10, SAS institute Inc, Cary, NC) and Microsoft Office (2010 Microsoft corporation, Redmond WA).

RESULTS

Characteristics of the subjects in the study

Table 1 shows the basic characteristics of the subjects included in the study. Thirty three percent of subjects were female (n=32/97) and the mean age of the subjects was 51 years. Amongst the subjects, ~23% (n=22) reported an ‘allergic reaction’ with aspirin and ~61% (n=59/97) 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) while those who did not were designated as aspirin tolerant (AT). Amongst those with H-AS, 45% were females while in those did not endorse such history, 29% were females (P=0.19). The mean age of patients in the two groups were different, those with H-AS being younger (Mean . 45.7 years) than those in the AT group (Mean . 52.5 years, P =0.04).

Select laboratory parameters and clinical variables between these two groups of patients (Table 1) are also shown as part of baseline comparison. Pre-surgical peripheral eosinophil

count was similar between the H-AS group (mean 463 cells/mm^3) and AT group (437 cells/mm^3, P=0.74). The highest recorded eosinophil count was greater in H-AS (mean 916 cells/mm^3) compared to AT (mean 574 cells/mm^3, P=0.002). Levels of Vitamin D in H-AS patients were mean 25.7 ng/ml compared to mean 33.9 ng/ml in the AT group (P=0.11). There were no significant differences between total serum IgE levels or atopic status between the two groups. All patients in H-AS group had nasal polyps (100%, n=22) compared to 80% in AT group (P=0.01). Mean Lund-Mackay (LM) CT scores for sinus disease was 15.7±0.9 in H-AS group compared to AT group (mean 13.7±0.5, P=0.06). Finally, there was a significant difference in total pre-surgical SNOT-22 scores between the two groups, with H-AS patients having a total SNOT-22 score (mean 57.8) compared to the AT group (mean 39.6, P<0.001).

Since H-AS subjects had quantitative differences in total SNOT-22 score compared to 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 two groups (Table 2). In H-AS subjects: need to blow nose (Q1), sneezing (Q2), runny nose (Q3), post nasal 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 to AT subjects (P<0.05). Using adjusted significance values (Bonferroni) for multiple variable comparisons and significance of 0.05, only need to blow nose (Q1, P<0.002), runny nose (Q3, P<0.006), thick nasal discharge (Q6, P=0.01), ear pain/pressure (Q9, P=0.05) and (lack of) sense of taste/smell (Q21, P<0.002) were higher between H-AS subjects and the AT group.

Next, we wished to study if CRS symptoms in the entire cohort demonstrated inherent patterns of association of individual symptom elements without stratification using pre-supposed criteria. To this end, we performed an *unsupervised* pairwise correlation analysis to investigate co-occurrence of CRS symptoms without a presupposition bias (Figure E1). Sinonasal symptoms (questions 1–6 and 21–22) clustered together. Another group of symptoms related to the ear (questions 7–10); emotion (questions 19, 20); and sleep and function related 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 based on magnitude and differential expression and relate to history of aspirin sensitivity

Since univariate analysis of H-AS and AT showed differences in select items, we wished to determine if symptom analysis could differentiate subjects. To this end, we used *unsupervised* method of bipartite network graphs and cluster analysis. Select steps in generation of the bipartite graph are shown in the supplemental section (Figure E2). A connected bi-partite network graph depicts the connection between all CRS patients and all of their individual SNOT item responses as nodes. Random spatial allocation of each type of node is generated (supplemental Figure E2A, patients as grey 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 E2B). The larger symptom nodes thus represent higher cumulative frequencies of those symptoms, while the larger patient nodes represent patients with higher disease burdens.

The resultant graph is a mathematical model depicting associations (Supplemental figure E3) 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 based on the pattern of symptom expression (dendrogram, figure. E3 inset) and revealed 5 clusters (named A–E). As the network itself is ignorant of the ASA 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 one patient of 23 (4.3%) in cluster E and none of ten (0%) patients in cluster D were H-AS This suggests that groups of symptoms may be able to aid in determining the likelihood of aspirin sensitivity. Furthermore, aspirin sensitivity was confirmed in 11/14 H-AS patients in clusters A, B, and C who underwent aspirin challenges (Table 3).

Cluster A had high affinity to both the sinonasal and non-sinonasal symptoms (P=1) and formed the dense core of the network. Clusters B and C were significantly closer to sinonasal symptoms (P<0.001) but differed in the proximity to the non-sinonasal symptom cluster. Cluster D and E comprised of mostly patients in the periphery of the network with cluster D significantly closer to non-sinonasal symptoms (P<0.001) while cluster E was associated with sinonasal symptoms (P<0.001). Thus *unsupervised learning* reveals the heterogeneity in pre-surgical 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 amongst symptom-based clusters

We then wished to analyze other clinical parameters including asthma or atopy amongst 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 3). The clusters themselves were fairly matched in age and gender composition. Cluster A patients had the highest total SNOT-22 scores (90.8 ± 3), while cluster E had the lowest total SNOT-22 scores (16.4 ± 2), and the total SNOT-22 differences were significant (P<0.001) between the groups except for between cluster C and cluster D. The Lund McKay CT sinus score was highest in cluster C (mean 15.8) and lowest in cluster A (mean 11.6, overall P=0.02). As to the medication usage history, overall corticosteroid usage was found to be different across groups (P=0.02). Three of 10 (30%) patients in group D had received systemic corticosteroids prior to SNOT-22 assessment (day 48, 51 and 14). two of 6 (33%) in group A received prednisone (day 9 and on day of) assessment of SNOT-22. Of those in cluster D that received systemic corticosteroids the total SNOT-22 was 33.3 ± 6 compared to those that did not 39.5 ± 4 (P=0.19). Sixty-seven percent (4 of 6) subjects in cluster A had nasal polyps compared to 100% nasal polyposis in cluster D (10 of 10, overall P=0.06). The mean total SNOT-22 scores at first follow up were 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=0.006). First SNOT-22 assessment post-surgery showed significant improvement in all clusters (P<0.001) except E (P=0.50) compared to pre-surgical scores. The mean SNOT-22 scores at second follow-up were 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<0.001). Clusters B, C and D continued to maintain symptom resolution at second visit post-surgical intervention (median 97 days) while cluster A had an increase in SNOT-22 scores between the first and second postoperative visits. This difference was however, not significant (P=0.52).

DISCUSSION

Chronic rhinosinusitis has a profound impact on quality of life in patients. There have been several well validated tools which 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 one at a time between preassigned groups, does not offer the complete picture of symptom burden and inter-relationship of symptoms in CRS. As such, we conducted an unsupervised analysis using network graphs to reveal the patterns of symptom in CRS patients.

In this study using a standardized pre-surgical questionnaire (SNOT-22), we identify five clusters of CRS patients. 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 as 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 CRS patients to be significantly different in patients with aspirin sensitivity versus those without [16, 17]. We report similar findings, however note that pre-surgical eosinophil counts did not differ between those CRS patients with H-AS or AT group, but there was significant serum eosinophilia in H-AS subjects when the highest recorded eosinophil count was compared between the two groups. We speculate that optimization of medical intervention prior to surgical intervention may have accounted for the lack of difference between the pre-surgical eosinophil numbers. Serum IgE or atopy did not correlate with history of aspirin sensitivity which confirms previous findings[17]. In regards to symptoms, univariate analysis revealed that five elements of the SNOT-22 questionnaire were significantly different between the H-AS 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 post-surgery but there is often under-reporting of this history[18], or a definitive history is not available in some cases (up to 50% in one report)[19]. Thus there is a need for identification of clinical features, either singly or in a group, that can aid in predicting presence or absence of aspirin sensitivity, especially in those undergoing surgery. Recent studies do hint towards 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 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 pre-supposition is an important and novel contribution of unsupervised analyses which complements the 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 CRS patients 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 Lund McKay 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 system[24] remains to be seen.

Prior studies have shown mixed influences of aspirin sensitivity on surgical outcomes[6, 25]. Symptom-based clustering revealed differences in post-surgical response amongst the groups. Patients with lowest burden of disease and sino-nasal predominant symptoms preoperatively (cluster E) did not improve significantly post procedure compared to clusters A–D which had great improvement in total SNOT-22 score post-surgery. Thus these patients represent a group whose clinical symptoms apparently respond to medical therapy prior to 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 asthmatics (75%) was seen in cluster B, which also demonstrated aspirin sensitivity, sino-nasal symptom affinity, relative eosinophilia and nasal polyposis, although the. Differences in proportions of asthmatics across all the clusters were not significant. There are a few possible reasons which 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 over-reporting of asthma status in the cohort. Secondly, 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. Thirdly, the SNOT-22 score used for network analysis was specifically a pre-surgical symptom score with the expectation that the patients were optimized for surgery and presumably not at their worst. Thus, while the magnitude or quality of the symptom burden correlated well to the history of aspirin sensitivity, asthma status did not in our study. Finally, the study may not be powered to show differences in asthmatics vs non-asthmatics 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 total SNOT-22 was more in one group (B) than the other. Whether this is related to other factors (such as comorbidities) influencing symptom perception is intriguing. Wasan et al have reported an association between psychiatric comorbidities and increased symptoms in CRS[26]. 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 post ESS. Remarkably, clusters D and E have similar CT scan LM scores but very different symptom perceptions (systemic, i.e. non-sinonasal versus local, i.e. sinonasal). Whether this could relate to systemic effects of local inflammation[27] in one group or the effect of other factors is a question for future study.

There are a few limitations to the study. This was a group of patients referred to a tertiary care facility and the study population does not reflect the trends in the general population. Secondly, 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 visit 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. In order to be specific in the timing of collection of SNOT-22 symptoms, the score most immediate prior to surgery and two responses after surgery was used for the analysis. Thirdly, 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 NSAIDS. Fourthly, 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 pre-surgical symptoms in CRS patients. Unsupervised cluster analysis of SNOT-22 questionnaire has been recently utilized to derive reduced meaningful ‘factors’ as they relate to clinical characteristics [9, 10]. In their study Sedaghat et al have used principal component analysis of SNOT-22 to describe four components in patient history (symptoms related to sleep, nasal, otologic, and emotion) as they relate to clinical characteristics[10] while in the study by Soler et al SNOT-22 was part of a group of variables (including depression and SF-12 questionnaires)[9]. Network graphs are unique as 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 which employed 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) as well as variables (and their clusters) [hence *Bipartite*] and the relationships between them. Bipartite network graphs are being increasingly employed to newer fields of application to acquire a high level view of data e.g. 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 current 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 CRS patients and indicate that proper recognition of these differences may assist a clinician to institute individualized treatment regimens specifically tailored to subgroups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported by the Mayo Foundation and NIH grant R56 AI49235 (HK)

ABBREVIATIONS

AT	aspirin-tolerant
CRS	chronic rhinosinusitis
EES	endoscopic sinus surgery
H-AS	history of aspirin sensitivity
IQR	inter quartile range
SNOT-20	20-item sinonasal outcome test
SNOT-22	22-item sinonasal outcome test
WDC	Weighted degree centrality

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HIGHLIGHT BOX

What is already known about this topic?

Patients with chronic rhinosinusitis with aspirin sensitivity have a higher disease burden and poorer post-surgical 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?

CRS patients exhibit a heterogeneous symptom burden with varying emphasis on individual SNOT-22 symptoms. This heterogeneity was associated with history of ASA sensitivity and was related to treatment outcomes.

How does this study impact current management guidelines?

The study result facilitates recognition of symptom heterogeneity in CRS, which should aid in the work up of CRS and in the prediction of aspirin sensitivity and which relates to response to treatment such as surgery.

Table 1

Characteristics of subjects in study

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

	Number	Percent
Gender (females)	32/97	33
Age in years (mean ± SEM)	51 ± 1.4	
History of aspirin sensitivity	22/97	23
Physician diagnosed asthma	59/97	61

	No history of ASA sensitivity (AT)	History of ASA sensitivity (H-AS)	p-value
Gender Females (%)	22 of 75 (29)	10 of 22 (45)	0.19
Age (mean ± S.E) (yrs)	52.5 ± 2	45.7 ± 3	0.04
Peripheral eosinophil count Pre-surgical, mean cells/cu. mm	437 ± 38	463 ± 69	0.74
Peripheral eosinophil count Highest, mean cells/cu. mm	574 ± 52	916 ± 94	0.002
Serum Vit. D lowest, mean ng/ml	33.9 ± 2	25.7 ± 5	0.11
Serum IgE, Mean IU/l	361 ± 87	371 ± 143	0.95
Allergen sensitivity by skin test (any) (%)	35 (58)	13 (70)	0.41
Asthma (%)	38 (50%)	21 (95)	<0.001
Nasal polyps (%)	60 (80)	22 (100)	0.01
Lund McKay Score CT sinus (total), presurgical	13.7 ± 0.5	15.7 ± 1	0.06
Total SNOT-22 score pre-surgery	39.6 ± 2	57.8 ± 4	<0.001

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

Table 2

Comparison of individual SNOT-22 elements between H-AS and AT groups.

Comparison of individual SNOT-22 item scores between CRS patient with history of aspirin sensitivity (H-AS) and those without (AT). 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 0.05 considered significant after correction.

Item	Description	H-AS Mean ± SEM	AT Mean ± SEM	P-value	Corrected
1	**Need to blow nose**	**3.7 ± 0.3**	**2.3 ± 0.2**	**<0.001**	**<0.001**
2	Sneezing	2.2 ± 0.3	1.5 ± 0.2	**0.03**	0.66
3	**Runny nose**	**3.6 ± 0.3**	**2.1 ± 0.2**	**<0.001**	**<0.006**
4	Cough	2.0 ± 0.3	1.7 ± 0.2	0.34	
5	Post nasal discharge	3.2 ± 0.3	2.4 ± 0.2	**0.03**	0.66
6	**Thick nasal discharge**	**3.6 ± 0.4**	**2.2 ± 0.2**	**<0.001**	**0.01**
7	Ear fullness	2.6 ± 0.4	1.5 ± 0.2	**0.008**	0.17
8	Dizziness	1.4 ± 0.3	0.9 ± 0.2	0.13	
9	**Ear pain/pressure**	**1.4 ± 0.2**	**0.5 ± 0.1**	**0.002**	**0.05**
10	Facial pain/pressure	2.2 ± 0.3	1.8 ± 0.2	0.33	
11	Difficulty falling asleep	2.0 ± 0.3	1.4 ± 0.2	0.13	
12	Waking up at night	2.5 ± 0.3	2.0 ± 0.2	0.13	
13	Waking up tired	2.8 ± 0.3	1.8 ± 0.2	**0.01**	0.22
14	Lack of good night's sleep	3.0 ± 0.3	2.2 ± 0.2	**0.03**	0.66
15	Fatigue during the day	2.7 ± 0.4	2.1 ± 0.2	0.10	
16	Reduced productivity	2.3 ± 0.3	1.7 ± 0.2	0.14	
17	Reduced concentration	2.3 ± 0.4	1.8 ± 0.2	0.21	
18	Frustrated/restless/irritable	2.3 ± 0.3	1.6 ± 0.2	0.08	
19	Sad	1.1 ± 0.2	0.5 ± 0.1	**0.01**	0.22
20	Embarrassed	1.3 ± 0.3	0.5 ± 0.1	**0.004**	0.08
21	**Sense of taste/smell**	**4.6 ± 0.4**	**2.9 ± 0.2**	**<0.001**	**<0.002**
22	Blockage/congestion of nose	4.0 ± 0.3	3.0 ± 0.2	**0.008**	0.17

H-AS: History of aspirin sensitivity, AT: No history of aspirin sensitivity. P<0.05 considered significant.

Table 3

Inter-cluster comparison of clinical characteristics between the symptom-based clusters

Inter cluster comparison between clinical variables. Overall significance between groups depicted with $p<0.05$ considered significant.

	Cluster A (n=6)	**Cluster B (n=28)**	**Cluster C (n= 30)**	**Cluster D (n=10)**	**Cluster E (n=23)**	**p**
Age in years (mean ± SEM)	47 ± 6	48.5 ± 3	52.7 ± 3	47.2 ± 4	54.6 ± 3	0.40
Gender (Women, %)	4 (67)	11 (39)	8 (27)	3 (30)	6 (26)	0.32
Vitamin D3 ng/ml (mean)	23.4 ± 7	30.7 ± 4	35.8 ± 4	27 ± 6	38.3 ± 5	0.33
Eosinophil cells/mm^3 (Mean)	472 ± 195	835 ± 87	601 ± 81	507 ± 145	607 ± 100	0.15
Lund McKay Score CT Total, pre-surgical (mean ± SEM)	11.6 ± 2	14.5 ± 1	15.8 ± 1	12.4 ± 1	12.8 ± 1	0.02
Total pre-surgical SNOT-22 score	90.8 ± 3	62 ± 1	40.3 ± 1	37.7 ± 2	16.4 ± 2	< 0.001
Symptom cluster affinity	Both	Sinonasal	Sinonasal	Non Sinonasal	Sinonasal	
History of ASA sensitivity (%)	3 (50)	11 (39)	7 (23)	0 (0)	1 (4)	0.006
Proportion of patients with h/o ASA sensitivity that were challenged and were positive	1 of 1 (100%)	6 of 8 (75%)	4 of 5 (80%)	-	0	
Nasal polyposis	4 (67)	27 (96)	24 (80)	10 (100)	17 (74)	0.06
Asthma (%)	3 (50)	21 (75)	16 (53)	6 (60)	13 (56)	0.47
Atopy (%)*	2 (50)	12 (54)	14 (56)	8 (100)	11 (61)	0.20
Any systemic corticosteroid use (%)**	2 (33)	1 (4)	1 (3)	3 (30)	2 (8)	0.02
Post-surgical followup						
Total post-surgical SNOT-22 score (Visit 1)	44 ± 7	21.3 ± 3	24 ± 3	16.8 ± 5	12.9 ± 4	0.006
Total post-surgical SNOT-22 score (Visit 2)	55.6 ± 9	20.6 ± 4	27 ± 4	9.5 ± 6	13.6 ± 4	<0.001

* 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 months or oral prednisone within1 month of assessment