Cluster analysis of chronic rhinosinusitis suggests gender-based differences

Jurlin, Lana; Gregurić, Tomislav; Baudoin, Tomislav; Grgić, Marko Velimir; Pažanin, Leo; Košec, Andro; Scadding, Glenis; Kalogjera, Livije

Source / Izvornik: **ORL, 2018, 81, 1 - 9**

Journal article, Accepted version
Rad u časopisu, Završna verzija rukopisa prihvaćena za objavljivanje (postprint)

https://doi.org/10.1159/000492966

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:781899

Cluster Analysis of Chronic Rhinosinusitis Suggests Gender Based Differences

Running head: Is Chronic Sinuitis Gender Dependent?

Lana Jurlin, MD[a], Tomislav Gregurić, MD, PhD[b], Tomislav Baudoin, MD, PhD[c], Marko Velimir Grgić, MD, PhD[c], Leo Pažanin, MD[d], Andro Košec, MD, PhD[c], Glenis Scadding, MA, MD, FRCP[e], Livije Kalogjera, MD, PhD[c]

a) Department of Otorhinolaryngology, General Hospital Varaždin, Croatia

b) Department of Radiology, University Hospital Centre Sestre milosrdnice, Vinogradska cesta 29, Zagreb, Croatia

c) Department of Otorhinolaryngology and Head and Neck Surgery, Zagreb School of Medicine, University Hospital Centre Sestre milosrdnice, Zagreb, Croatia

d) Department of Clinical Pathology Ljudevit Jurak, University Hospital Centre Sestre milosrdnice, Zagreb, Croatia

e) Royal National TNE Hospital, London, United Kingdom

Author correspondence:

Andro Košec, MD, PhD, Zagreb School of Medicine, University Hospital Centre Sestre milosrdnice, Vinogradska 29, 10000 Zagreb, Croatia; E-mail: andro.kosec@yahoo.com, mobile phone 00385-99-2029-299, Fixed phone: 003851-3787-451

Abstract

Purpose: We aimed to evaluate the interaction between the overall severity of chronic rhinosinusitis (CRS) before treatment and subjective improvement following surgical or medical treatment.

Procedures: A group of 97 patients with CRS completed the visual analog scale (VAS) symptom scores and Sino-Nasal Outcome Test 22 (SNOT-22) questionnaire at the moment of their sinus computerized tomography (CT) scan. Data were analyzed with two-step cluster analysis based on gender, polyp presence, CT scan and VAS scores for symptoms.

Results: There were three clusters: the first cluster with 37 female patients with CRS without nasal polyps (CRSsNP), the second cluster formed a cohort of 30 patients with CRS and NP, CRSwNP (15 male and 15 female); and third cluster had 30 male patients with CRS without NP (CRSsNP). Different symptom patterns between clusters were identified. After adjustment for polyp presence, gender, eosinophilia ($p = 0.021$) and the SNOT-22 score ($p=0.005$) were found to be better outcome predictors than the CT score ($p = 0.26$).

Conclusion: Long-term patient satisfaction is significantly associated with the subjective symptoms' severity prior to treatment: postnasal drip and overall disease severity (SNOT-22 score), but not with the objective severity of the disease (CT score and inflammation).

Keywords: chronic rhinosinuisitis; nasal polyps; SNOT-22; computerized tomography; VAS score

Introduction

Chronic rhinosinusitis (CRS) is a complex syndrome which has a significant impact on health-related quality of life (HRQL). Based on endoscopic studies, CRS is divided into two phenotypes: with and without nasal polyps (CRSwNP and CRSsNP, respectively). [1] Recent studies indicate that phenotypes and some confounders, like comorbidities and gender, play a major role in the definition of the pattern of CRS symptoms and HRQL impairment. [2, 3] The overall subjective severity of the disease may help to predict the outcomes of surgical treatment. [4, 5, 6, 7] The most common objective severity staging is based on CT scans, rather than on endoscopy scores, however, radiographic staging does not correlate with symptoms, nor does it help in predicting subjective improvement after sinus surgery [8]. Objective outcome measures (endoscopy, CT score, eosinophilic inflammation, osteitis) correlate significantly among themselves. However, correlation between subjective (HRQL) and objective outcomes is often absent or mild. Furthermore, several papers have suggested that CRS patients with psychiatric distress (somatization, anxiety, depression) or those exposed to chronic psychological stress, report with more severe CRS symptoms and higher HRQL impairment. [9, 10]

Several treatment options are available, but approximately 20% of patients with CRS do not respond well to the recommended treatment. [11] It is suggested that, besides differences in symptom patterns, major phenotypes differ in the response to surgical or combined (surgical and drug) treatment. [12] Early recognition of patients who are refractory to the long term medical and surgical treatment may prevent repetitive unnecessary sinus surgery and potential complications of such procedures.

This study was done to evaluate the interaction between CT scores, subjective disease severity, based on symptom scores and HRQL impairment, and subjective improvement after drug or

surgical treatment. The secondary aim was to evaluate the interaction between severity of inflammation, based on inflammatory cell infiltration in sinus mucosa collected at surgery, in patients where such samples were available for analysis, with Patient Response Rating Scale (PRRS) related to overall improvement after surgical treatment.

Material and methods

This prospective observational study was conducted at the Department of Otolaryngology and Head and Neck Surgery and at the Department of Radiology, University Hospital Centre Sestre milosrdnice from January 2013 to February 2016. It was approved by the Ethics Committee of University Hospital Centre Sestre milosrdnice, Zagreb School of Medicine, adhering to the Helsinki Declaration Revision of 1989. All patients who met the European Position Paper on Rhinosinusitis and Nasal Polyps 2012 (EPOS 2012) clinical criteria for CRS and provided informed consent were approved for entry into the study. [1] Symptom based diagnosis was confirmed by evidence of objective signs of the disease based on endoscopy and CT scans. CT scans were taken as a part of the preoperative procedure or as a diagnostic tool in evaluation of patients with CRS. Patients were excluded if they had acute exacerbation of rhinosinusitis, trauma or tumors of the nasal/sinus cavities, cystic fibrosis, granulomatous disease affecting the sinus or nasal cavity mucosa, or age <18 years.

Demographic information such as age and gender, duration of symptoms, history of previous surgery, concurrent asthma, and allergy to relevant airborne allergens, medication history, was collected. For patients with seasonal allergic rhinitis, CT scans and questionnaires were taken at least 2 months after the pollen season. The extent of sinus opacification was graded according to the Lund-Mackay staging system. [13] Each patient was asked to fill out two questionnaires to

grade their subjective symptoms. The visual analogue scale (VAS) for major and minor symptoms was implemented according to the recommendation by the Rhinosinusitis Task Force. [14] The symptoms assessed by the VAS were: nasal discharge, nasal obstruction, postnasal discharge, smell impairment, facial pain/pressure, facial fullness, headache, dental pain, halitosis, cough, ear pain/fullness and fatigue. Patients graded their subjective symptoms with VAS marking the intensity of the symptoms on a straight line from 0 to 10cm.

Sino Nasal Outcome Test 22 (SNOT-22) is the most commonly used validated disease specific questionnaire that provides a quantitative measure of symptoms severity and health related quality of life for patients with CRS. Intensity of each symptom is scored on a 0-5 Likert scale, whereby a score of 0 signifies no symptoms and the maximum value of 5 signifies the most severe symptoms. [10, 11] CT scans of the paranasal sinuses were taken using a multidetector CT scanner with spiral mode scanning and axial cuts of 0.5 mm thickness, and afterwards evaluated using multiplanar reconstruction images. A standard Patient Response Rating Scale (PRRS) was used to classify the subjective effect of the treatment in the period of 1 to 2 years after surgery and/or other medical treatment. [15] Patient rated effects of treatment from 1 to 5: 1- desperately worse, 2-worse, 3- no change, 4-improvement (although symptoms are present) and 5- cured (no symptoms present).

After the follow-up period of 1 to 2 years, patients were evaluated through telephone surveys for the overall improvement after treatment, either drug or surgical treatment, using the PRRS.

In patients with surgical samples available, the semi-quantitative scoring system was used to grade intensity of inflammation in sinus mucosa, for eosinophils and mononuclear cells (0- no eosinophils; 1= up to 10 eosinophils per high power field (HPF), 2= 10-20 eosinophils per HPF; 3 = 20 -100 eosinophils per HPF; 4 = more than 100 eosinophils per HPF). [16]

In order to define further subgroups within CRS, related to subjective and objective disease severity and symptoms pattern, we performed two-step cluster analysis which included two most important categorical characteristics: nasal polyps and gender, objective severity of disease (Lund-Mackay score) and VAS scores for symptoms based on major and minor symptoms (nasal secretion, postnasal secretion, smell impairment, nasal obstruction, facial pain/fullness, headache and fatigue) prior to treatment. Two step cluster analyses is an exploratory statistical tool designed to reveal grouping within datasets that are not otherwise apparent. It can handle categorical and numerical variables used in analyses in the same time. When calculating differences between clusters we used Chi-square test for categorical variables and Kruskal Wallis nonparametric statistical test for numerical variables. Significant differences between variables were post hoc tested with Mann Whitney U statistical test. A linear regression analysis was performed to determine the independent relationship between PRRS score as dependent variable and VAS symptom scores, SNOT-22 score and Lund-Mackay score as independent variables. In order to control the potential influence of major phenotype characteristics as gender and nasal polyp presence, these variables were included as covariates in the linear regression model. Data were quantified through regression coefficients separately for overall patients and for group of patients on medical or surgery therapy performed with a statistical significance set at a $p < 0.05$. Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS version 23.0, Chicago, IL, USA).

Results

From a total of 110 CRS patients evaluated, 97 patients were subjected to two-step cluster analyses, as others had missing variables and were excluded from the study. The analysis

detected cohort differences in CRS clustering according to gender and polyp presence, coupled with VAS scores for major and minor symptoms. Whereas polyp patients were in one cluster, regardless of gender, those without polyps separated into two distinct gender- based clusters with the female group having significantly more asthma and tending to be older. (Tables 1 and 2). Significant differences were found in comorbidities between three clusters. Asthma, allergy and ASA intolerance were more common in patients with nasal polyps (cluster 2). The differences between the three clusters for VAS symptom scores are shown in Figure 1. As VAS scores were used as continuous variables for two-step cluster analysis, statistical differences between clusters for symptoms were not calculated. Box plot distributions of Lund-Mackay scores and PRRS scores are shown in Figure 2. Lund-Mackay score was highest in the CRSwNP cluster. SNOT-22 score showed no significant differences between clusters (Table 2).

When analyzing the whole study cohort, significant difference in PRRS scores between the 3 clusters was found ($p = 0.025$), but in the subgroups of patients with medical or surgical therapy performed, no difference was detected (Table 3). However significantly higher PRRS score was found in operated patients compared to those with medical management only ($p = <0.001$) when the whole cohort was considered.

In the surgically treated CRS patients, the highest inflammatory cell infiltration was found in mucosal samples in cluster 2 (CRSwNP patients) with a significant difference between clusters ($p = 0.001$) for eosinophils and total inflammatory cells (Table 3).

Independent associations of PRRS score with SNOT-22, Lund-Mackay and symptom scores are presented in Table 4. Lower initial SNOT-22 scores in overall patients and in patients on medical treatment were significantly associated with higher PRRS score ($p = 0.005$ and $p = 0.001$ respectively) but not in patients after surgical therapy ($p = 0.113$).

Lower postnasal secretion scores were significantly associated with higher PRRS in overall patients (p =0.012) and in patients treated medically (p = 0.016).

Discussion

The severity of chronic rhinosinusitis (CRS) is a result of the interaction of the debilitating symptoms and several confounders which have an additional impact on HRQL. [17] Two-step cluster analysis revealed 3 almost symmetric clusters in our cohort of CRS patients when clustering was done with 2 major confounders (gender and polyp presence) and the combination of VAS and CT scores as measures of severity. Interestingly there appear to be two different gender- based groups of CRSsNP patients, whereas CRSwNPs is a single group, regardless of gender. The cluster with CRSwNP had significantly worse obstruction, smell and SNOT-22 scores than both other clusters.

We found higher scores for pain and fatigue in females suffering from CRSsNP, than in the other two clusters, and these results were not related to CT scan scores or inflammation. Comparing gender- related differences in SNOT-22 in the two CRSsNP phenotypes, clusters 1 and 3, the mean scores for all items were worse in female patients, except for nasal obstruction. Gender appears a major confounder affecting overall disease severity in this phenotype and it may be that the pathogenesis of CRSsNPs is different in females. The higher occurrence of asthma and the appearance of AERD among these subjects suggest a possible *forme fruste* of nasal polyposis, rather than a problem with immune deficiency. Male patients in the CRSsNP phenotype (cluster 3) also have significantly better improvement rate than female CRSsNP (cluster 1). On the other hand, the subjective outcomes in CRSwNP patients were not affected by gender.

It has been demonstrated that severity of CRS in a disease specific questionnaire, such as SNOT-22, is a good predictor of the patient's decision for sinus surgery and for the short-term subjective improvement after surgical treatment for CRS. [20] Meta-analysis of 4 randomized trials comparing different methods of medical and surgical treatment in CRSwNP has shown no difference in patient reported outcomes and HRQL, however, as studies in the meta-analysis were of very low quality, further evidence is still needed. [21] Although we have demonstrated a greater benefit of surgical treatment on our cohort, we cannot rely on this data, as the study was not randomized. Obviously the selection bias of our study group has demonstrated significantly better improvement in the surgical group and did not confirm higher values of SNOT-22 in patients who decided for surgery. Unfortunately, the type of phone survey did not enable us to recognize why patients with higher overall disease severity (high SNOT-22 score) were not assigned to surgery. Surgery was performed in more than 80% of the patients whose rating improved or were cured, while more than 70% of patients who remained unchanged or got worse had medical treatment only in our cohort.

Only postnasal drip and SNOT-22 scores prior to treatment, used as a measure of overall disease severity, seem to affect long-term outcomes, and we may speculate from the results of the regression analysis that they seem to be predictors of worse outcomes. It indicates that difficult-to-treat patients, who are unresponsive to all kinds of treatment, have the interaction of many factors which influence the overall CRS severity, not necessarily only related to the disease itself. [22]

We have not confirmed that higher CT scores have prognostic value on poor long term outcomes. Higher levels of mucosal hyperplasia, defined as higher sinus CT scores, and higher level of eosinophilic inflammation of sinus mucosa collected at surgery, seem to result in better

subjective improvement after surgery. Inflammation and CT scores are higher in CRSwNP, (in patients in cluster 1) which do not seem to result in worse outcomes compared to male CRSsNP patients, and are better than CRSsNP female patients. This confirms previous findings that CRSwNP patients demonstrate more satisfaction with surgical outcomes and suggests that comparison between mixed groups of CRs patients with and without nasal polyps is unhelpful. [12]

The major strength of our study is the observation of distinct clusters within CRS other than those previously recognized and the observation that gender- related differences are important in CRSsNPs, but not in CRS wNPs.

Conclusion

Long-term patient satisfaction, with medical or surgical treatment, is significantly associated with the subjective symptoms' severity prior to treatment: postnasal drip and overall disease severity (SNOT-22 score), but not with the objective severity of the disease (CT score and inflammation).

Conflict of interest: All authors declare that they have no conflict of interest.

References

[1] Fokkens WJ, Lund V, Mullol J, Bachert C, Alobid I, Baroody F et al: European Position Paper on Rhinosinusitis and Nasal Polyps 2012. A summary for otorhinolaryngologists. Rhinology 2012;50:1–12.

[2] Sedaghat AR, Gray ST, Caradonna SD, Caradonna DS: Clustering of chronic rhinosinusitis symptomatology reveals novel associations with objective clinical and demographic characteristics. Am J Rhinol Allergy 2015;29:100–5.

[3] Gregurić T, Trkulja V, Baudoin T, Grgić M, Šmigovec I, Kalogjera L: Differences in the Sino-Nasal Outcome Test 22 and visual analog scale symptom scores in chronic rhinosinusitis with and without nasal polyps. Am J Rhinol Allergy 2016;30(2):107-12.

[4] Kennedy J, Hubbard M, Huyett P, Patrie J, Borish L, Payne S: Sino-nasal outcome test (SNOT-22): a predictor of postsurgical improvement in patients with chronic sinusitis. Ann Allergy Asthma Immunol 2013;111(4):246-51.

[5] DeConde AS, Mace JC, Bodner T, Hwang PH, Rudmik L, Soler ZM et al: SNOT-22 quality of life domains differentially predict treatment modality selection in chronic rhinosinusitis. Int Forum Allergy Rhinol 2014;4:972–9.

[6] Hopkins C, Rudmik L, Lund V: The predictive value of the preoperative Sinonasal Outcome Test-22 score in patients undergoing endoscopic sinus surgery for chronic rhinosinusitis. Laryngoscope 2015;125(8):1779-88.

[7] Soler ZM, Hyer JM, Rudmik L, Ramakrishnan V, Smith TL, Schlosser R: Cluster analysis and prediction of treatment outcomes for chronic rhinosinusitis. J Allergy Clin Immunol 2016;137(4):1054-62.

[8] Bhattacharyya N: Radiographic stage fails to predict symptom outcomes afterendoscopic sinus surgery for chronic rhinosinusitis. Laryngoscope 2006; 116(1):18-22.

[9] Tomljenovic D, Pinter D, Kalogjera L: Perceived stress and severity of chronic rhinosinusitis in allergic and nonallergic patients. Allergy Asthma Proc 2014;35:398-403.

[10] Nanayakkara JP, Igwe C, Roberts D, Hopkins C: The impact of mental health on chronic rhinosinusitis symptom scores. Eur Arch Otorhinolaryngol 2013;270:1361–4.

[11] Hellings PW, Fokkens WJ, Akdis C, Bachert C, Cingi C, Dietz de Loos D et al: Uncontrolled allergic rhinitis and chronic rhinosinusitis: where do we stand today? Allergy 2013;68:1–7.

[12] Hopkins C, Slack R, Lund V, Brown P, Copley L, Browne J: Long-term outcomes from the English national comparative audit of surgery for nasal polyposis and chronic rhinosinusitis. Laryngoscope 2009;119(12):2459-65.

[13] Lund VJ, Mackay IS: Staging in rhinosinusitus. Rhinology 1993;31:183–4.

[14] Lanza DC, Kennedy DW: Adult rhinosinusitis defined. Otolaryngol Head Neck Surg 1997;117:S1–S7.

[15] Videler WJ, Badia L, Harvey RJ, Gane S, Georgalas C, van der Meulen FW et al: Lack of efficacy of long-term, low-dose azithromycin in chronic rhinosinusitis: A randomized controlled trial. Allergy 2011;66:1457–68.

[16] Grgić MV, Ćupić H, Kalogjera L, Baudoin T: Surgical treatment for nasal polyposis: predictors of outcome. Eur Arch Otorhinolaryngol 2015;272(12):3735-43.

[17] Rudmik L, Smith LT: Quality of Life in Patients with Chronic Rhinosinusitis. Curr Allergy Asthma Rep 2011;11:247–52.

[18] Abdalla S, Alreefy H, Hopkins C: Prevalence of sinonasal outcome test (SNOT-22) symptoms in patients undergoing surgery for chronic rhinosinusitis in the England and Wales National prospective audit. Clin Otolaryngol 2012;37(4):276-82.

[19] Dietz de Loos DAE, Hopkins C: Symptoms in Chronic Rhinosinusitis With and Without Nasal Polyps. Laryngoscope 2013;123:57–63.

[20] Soler ZM, Rudmik L, Hwang PH, Mace JC, Schlosser RJ, Smith TL: Patient-centered decision making in the treatment of chronic rhinosinusitis. Laryngoscope 2013;123(10):2341-6.

[21] Rimmer J, Fokkens W, Chong LY, Hopkins C: Surgical versus medical interventions for chronic rhinosinusitis with nasal polyps. Cochrane Database Syst Rev 2014; (12):CD006991. doi:10.1002/14651858.CD006991.pub2

[22] Tan BK, Chandra KR, Pollak J: Incidence and associated pre-morbid diagnoses of patients with chronic rhinosinusitis. J Allergy Clin Immunol 2013;131(5):1350–60.

Table captions

Table 1. Assignment of patients to clusters according to CRS phenotype and gender expressed as patients number per cluser (percentage).

Table 2. Demographic data and distribution of comorbidities among cluster groups, presented as medians (minimum - maximum) or percentages.

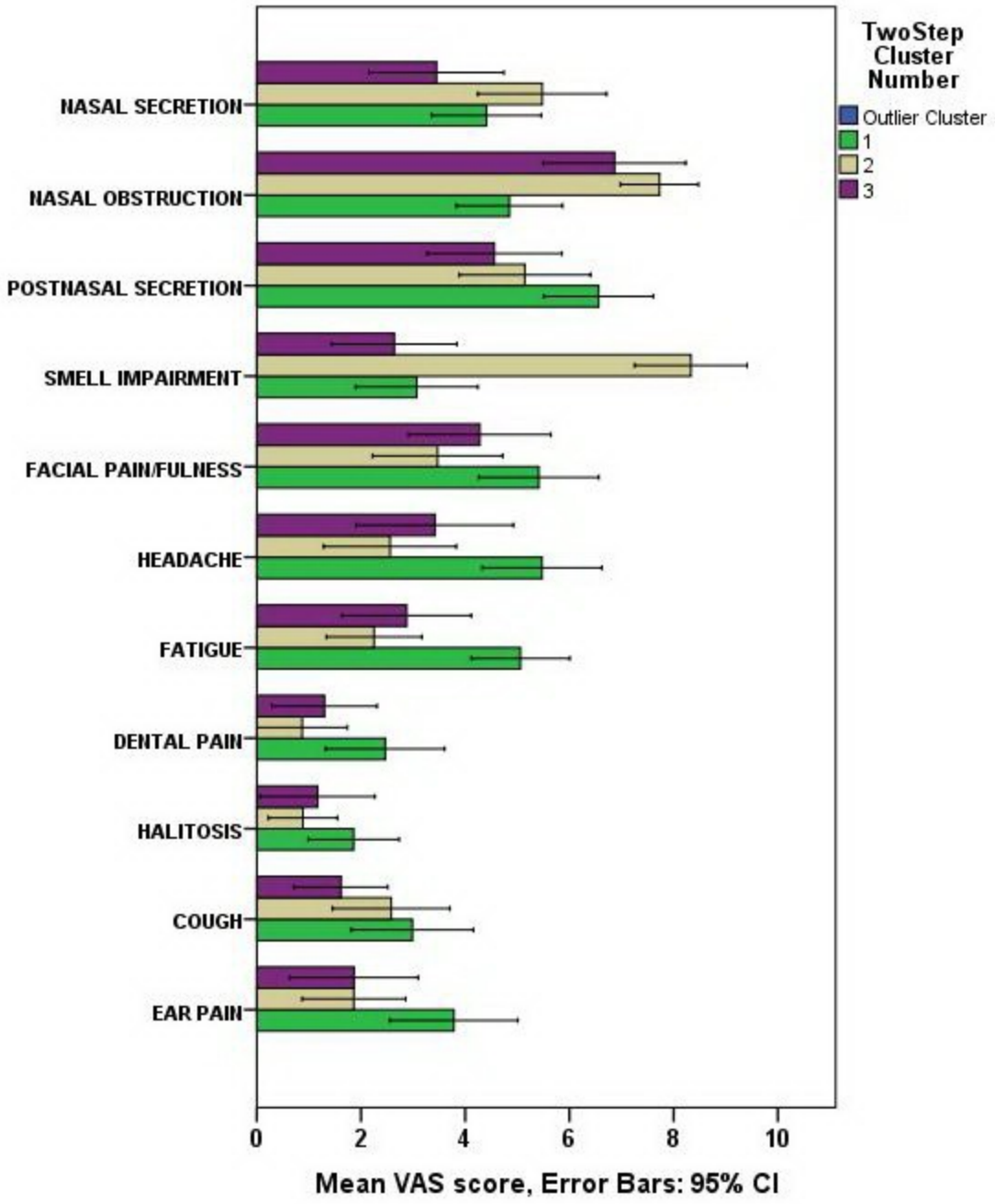
Table 3. Patients demographics, severity of inflammation and patient reporting outcomes among cluster groups depending on treatment modality

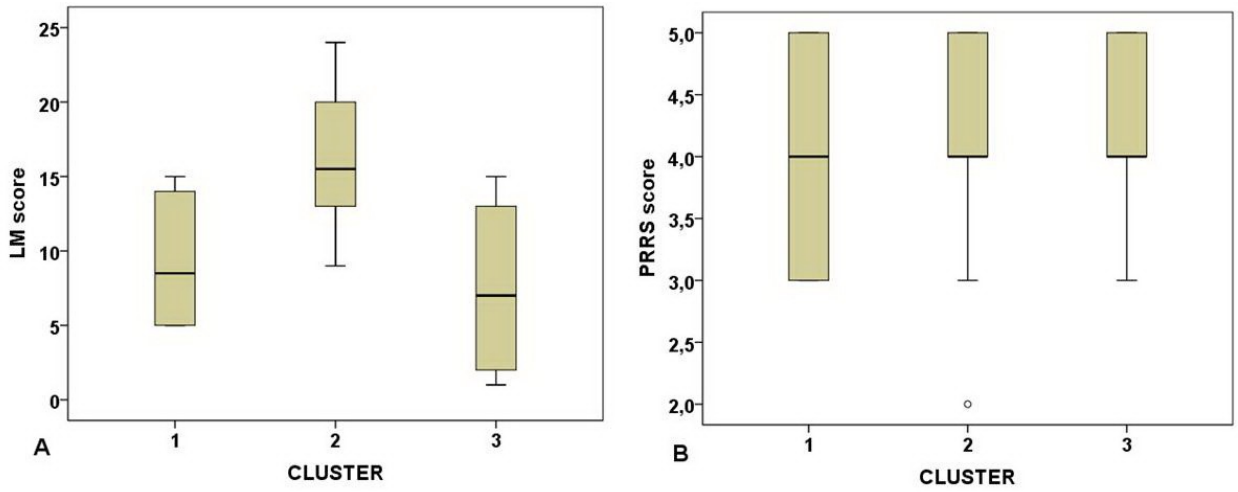
Table 4. Independent association between PRRS score and SNOT-22 score, LM score, symptom scores and cell infiltration before and after surgical or medical management

Figure legends

Fig. 1 VAS symptom scores presented as mean ± standard error for each cluster.

Fig. 2 Lund-Mackay (LM) scores and Patient Response Rating Scale (PRRS) scores per cluster presented as box-plots.


TwoStep Cluster Number
Outlier Cluster
1
2
3
NASAL SECRETION
NASAL OBSTRUCTION
POSTNASAL SECRETION
SMELL IMPAIRMENT
FACIAL PAIN/FULNESS
HEADACHE
FATIGUE
DENTAL PAIN
HALITOSIS
COUGH
EAR PAIN
0
2
4
6
8
10
Mean VAS score, Error Bars: 95% CI


LM score
25
20
15
10
5
0
1
2
3
CLUSTER
A
PRRS score
5,0
4,5
4,0
3,5
3,0
2,5
2,0
1
2
3
CLUSTER
B

Tables and Legends

Table 1. Assignment of patients to clusters according to CRS phenotype and gender expressed as patients number(percentage) per cluster.

		Cluster 1	Cluster 2	Cluster 3
Gender	Male N (%)	0 (0)	15 (33.3)	30 (66.7)
	Female N (%)	37 (71.2)	15 (33.3)	0 (0)
Clinical phenotype	CRSsNP N (%)	37 (71.2)	0 (0)	30 (66.7)
	CRSwNP N (%)	0 (0)	30 (66.7)	0 (0)
Patients	Total N = 97	37	30	30

CRSsNP Chronic rhinosinusitits without nasal polps, *CRSwNP* Chronic rhinosinusits with nasal polyps, *N* number of patients

Table 2. Demographic data and distribution of comorbidities among cluster groups, presented as medians (minimum - maximum) or percentages.

Variable	Cluster 1	Cluster 2	Cluster 3	P value

Age (years)	53.5 (40-62)	52.0 (26-70)	41.0 (19-68)	0.102
Symptom duration (years)	5 (0-40)	10 (0-30)	5 (1-15)	0.323
Asthma N (%)	9 (25.0)	14 (46.7)	3 (10.0)	0.006*
Allergy N (%)	12 (33.3)	17 (56.7)	8 (26.7)	0.042*
ASA intolerance N (%)	2 (5.7)	5 (17.2)	0 (0.0)	0.049*
Objective and subjective disease severity measures				
Lund-Mackay score	8.5 (5-15)	15.5 (9-24)	7 (1-15)	<0.001*

SNOT 22 (before treatment)		50,5 (23-67)	52,0 (26-70)	41,0 (19-68)	0.067
PRRS	(after treatment)	4.0 (3-5)	4.0 (2-5)	4 (3-5)	0.025*

ASA hypersensitivity to acetyl salicylic acid, *SNOT-22* Sinonasal Outcome test 22, *PRRS* Patient Response Rating Scale, *N* number of patients

*P value of <0.05 was considered statistically significant

Table 3. Patients demographics, severity of inflammation and patient reporting outcomes among cluster groups depending on treatment modality

	Surgical therapy			
	Cluster 1	Cluster 2	Cluster 3	P value

Patients N (%)	16 (43.2)	26 (86.7)	18 (60)	
Mononuclear cells	2.0 (1.0-2.5)	3.0 (1.0-4.0)	1.8 (1.0-3.5)	0.064
Eosinophil cells	1.0 (1.0-2.0)	3.0 (1.0-4.0)	1.5 (0.5-3.5)	0.001*
Mononuclear + eosinophil cells	3.0 (3.0-3.5)	5.5 (2.0-8.0)	4.0 (2.0-7.0)	0.001*
PRRS	4 (1-5)	4 (2-5)	4 (2-5)	0.270
		Medical therapy		
Patients N (%)	21 (56.8)	4 (13.3)	12 (40)	

PRRS	3 (1-5)	2.5(1-3)	3.5 (1-4)	0.165

PRRS Patient Response Rating Scale, *N* number of patients

*****P value of <0.05 was considered statistically significant

Table 4. Independent association between PRRS score and SNOT-22 score, LM score, symptom scores and cell infiltration related to surgical or medical management

	Estimate (95% CI)	P-value
Regression of SNOT 22 score vs. PRRS score		
Overall	-0.018 (-0.030, -0.006)	0.005*
In patients with surgery	-0.012 (-0.026, 0.003)	0.113
In patients without surgery	-0.027 (-0.042, -0.012)	0.001*
Regression of LM score vs. PRRS score		
Overall	0.028 (-0.021, 0.077)	0.255
In patients with surgery	0.020 (-0.029, 0.069)	0.428

In patients without surgery	-0.026 (-0.114, 0.063)	0.558
Regression of nasal secretion vs. PRRS score		
Overall	0.014 (-0.055, 0.083)	0.690
In patients with surgery	0.049 (-0.023, 0.121)	0.178
In patients without surgery	-0.103 (-0.202, -0.003)	0.043*
Regression of nasal obstruction vs. PRRS score		
Overall	-0.018 (0.092, 0.057)	0.638
In patients with surgery	-0.057 (-0.153, 0.039	0.237
In patients without surgery	-0.064 (-0.156, 0.027)	0.165
Regression of smell impairment vs. PRRS score		
Overall	0.029 (-0.038, 0.095)	0.392
In patients with surgery	0.003 (-0.076, 0.086)	0.935
In patients without surgery	-0.018 (-0.107, 0.071)	0.686
Regression of postnasal secretion vs PRRS score		
Overall	-0.083 (-0.148, -0.019)	0.012*
In patients with surgery	-0.059 (-0.013, 0.011)	0.096

In patients without surgery	-0.113 (-0.204, -0.022)	0.016*
Regression of facial pan/fulness vs. PRRS score		
Overall	-0.028 (-0.094, 0.038)	0.409
In patients with surgery	-0.069 (-0.138, -0.001)	0.047*
In patients without surgery	-0.037 (-0.138, 0.003)	0.458
Regression of headache vs. PRRS score		
Overall	-0.045 (-0.110, 0.020)	0.173
In patients with surgery	-0.044 (-0.114, 0.026)	0.218
In patients without surgery	-0.072 (-0.165, 0.021)	0.126
Regression of fatigue vs. PRRS score		
Overall	-0.052 (-0.131, 0.028)	0.202
In patients with surgery	-0.062 (-0.152, 0.028)	0.172
In patients without surgery	-0.046 (-0.157, 0.054)	0.403
Regression of cell infilitration vs PRRS score in patients with surgery		

Monoculear cells vs PRRS score	0.157 (-0.151, 0.466)	0.310
Eosinophil cells vs PRRS score	0.310 (0.010, 0.611)	0.043*
Mononuclear + eosinophil cells vs PRRS score	0.142 (-0.018, 0.303)	0.081

PRRS Patient Response Rating Scale, *SNOT 22* Sinonasal Outcome test 22, *LM* Lund-Mackay score

*****P value of <0.05 was considered statistically significant- better to use <0.025 because of multiple comparisons

Table 1. Assignment of patients to clusters according to CRS phenotype and gender expressed as patients number(percentage) per cluster.

		Cluster 1	Cluster 2	Cluster 3
Gender	Male N (%)	0 (0)	15 (33.3)	30 (66.7)
	Female N (%)	37 (71.2)	15 (33.3)	0 (0)
Clinical phenotype	CRSsNP N (%)	37 (71.2)	0 (0)	30 (66.7)
	CRSwNP N (%)	0 (0)	30 (66.7)	0 (0)
Patients	Total N = 97	37	30	30

CRSsNP Chronic rhinosinusitits without nasal polps, *CRSwNP* Chronic rhinosinusits with nasal polyps, *N* number of patients

Table 2. Demographic data and distribution of comorbidities among cluster groups, presented as medians (minimum - maximum) or percentages.

Variable	Cluster 1	Cluster 2	Cluster 3	P value
Age (years)	53.5 (40-62)	52.0 (26-70)	41.0 (19-68)	0.102
Symptom duration (years)	5 (0-40)	10 (0-30)	5 (1-15)	0.323
Asthma N (%)	9 (25.0)	14 (46.7)	3 (10.0)	0.006*
Allergy N (%)	12 (33.3)	17 (56.7)	8 (26.7)	0.042*
ASA intolerance N (%)	2 (5.7)	5 (17.2)	0 (0.0)	0.049*
Objective and subjective disease severity measures				
Lund-Mackay score	8.5 (5-15)	15.5 (9-24)	7 (1-15)	<0.001*
SNOT 22 (before treatment)	50,5 (23-67)	52,0 (26-70)	41,0 (19-68)	0.067
PRRS (after treatment)	4.0 (3-5)	4.0 (2-5)	4 (3-5)	0.025*

ASA hypersensitivity to acetyl salicylic acid, *SNOT-22* Sinonasal Outcome test 22, *PRRS* Patient Response Rating Scale, *N* number of patients

*P value of <0.05 was considered statistically significant

Table 3. Patients demographics, severity of inflammation and patient reporting outcomes among cluster groups depending on treatment modality

	Surgical therapy			
	Cluster 1	Cluster 2	Cluster 3	P value
Patients N (%)	16 (43.2)	26 (86.7)	18 (60)	
Mononuclear cells	2.0 (1.0-2.5)	3.0 (1.0-4.0)	1.8 (1.0-3.5)	0.064
Eosinophil cells	1.0 (1.0-2.0)	3.0 (1.0-4.0)	1.5 (0.5-3.5)	0.001*
Mononuclear + eosinophil cells	3.0 (3.0-3.5)	5.5 (2.0-8.0)	4.0 (2.0-7.0)	0.001*
PRRS	4 (1-5)	4 (2-5)	4 (2-5)	0.270
	Medical therapy			
Patients N (%)	21 (56.8)	4 (13.3)	12 (40)	
PRRS	3 (1-5)	2.5(1-3)	3.5 (1-4)	0.165

PRRS Patient Response Rating Scale, *N* number of patients

*P value of <0.05 was considered statistically significant

Table 4. Independent association between PRRS score and SNOT-22 score, LM score, symptom scores and cell infiltration related to surgical or medical management

	Estimate (95% CI)	P-value
Regression of SNOT 22 score vs. PRRS score		
Overall	-0.018 (-0.030, -0.006)	0.005*
In patients with surgery	-0.012 (-0.026, 0.003)	0.113
In patients without surgery	-0.027 (-0.042, -0.012)	0.001*
Regression of LM score vs. PRRS score		
Overall	0.028 (-0.021, 0.077)	0.255
In patients with surgery	0.020 (-0.029, 0.069)	0.428
In patients without surgery	-0.026 (-0.114, 0.063)	0.558
Regression of nasal secretion vs. PRRS score		
Overall	0.014 (-0.055, 0.083)	0.690
In patients with surgery	0.049 (-0.023, 0.121)	0.178
In patients without surgery	-0.103 (-0.202, -0.003)	0.043*
Regression of nasal obstruction vs. PRRS score		

Overall	-0.018 (0.092, 0.057)	0.638
In patients with surgery	-0.057 (-0.153, 0.039	0.237
In patients without surgery	-0.064 (-0.156, 0.027)	0.165
Regression of smell impairment vs. PRRS score		
Overall	0.029 (-0.038, 0.095)	0.392
In patients with surgery	0.003 (-0.076, 0.086)	0.935
In patients without surgery	-0.018 (-0.107, 0.071)	0.686
Regression of postnasal secretion vs PRRS score		
Overall	-0.083 (-0.148, -0.019)	0.012*
In patients with surgery	-0.059 (-0.013, 0.011)	0.096
In patients without surgery	-0.113 (-0.204, -0.022)	0.016*
Regression of facial pan/fulness vs. PRRS score		
Overall	-0.028 (-0.094, 0.038)	0.409
In patients with surgery	-0.069 (-0.138, -0.001)	0.047*
In patients without surgery	-0.037 (-0.138, 0.003)	0.458

Regression of headache vs. PRRS score		
Overall	-0.045 (-0.110, 0.020)	0.173
In patients with surgery	-0.044 (-0.114, 0.026)	0.218
In patients without surgery	-0.072 (-0.165, 0.021)	0.126
Regression of fatigue vs. PRRS score		
Overall	-0.052 (-0.131, 0.028)	0.202
In patients with surgery	-0.062 (-0.152, 0.028)	0.172
In patients without surgery	-0.046 (-0.157, 0.054)	0.403
Regression of cell infilitration vs PRRS score in patients with surgery		
Monoculear cells vs PRRS score	0.157 (-0.151, 0.466)	0.310
Eosinophil cells vs PRRS score	0.310 (0.010, 0.611)	0.043*
Mononuclear + eosinophil cells vs PRRS score	0.142 (-0.018, 0.303)	0.081

PRRS Patient Response Rating Scale, *SNOT 22* Sinonasal Outcome test 22, *LM* Lund-Mackay score

*P value of <0.05 was considered statistically significant- better to use <0.025 because of multiple comparisons