

Perceived stress and severity of chronic rhinosinusitis in allergic and nonallergic patients

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ABSTRACT

Chronic stress exposure carries greater risk of onset of atopic respiratory disorders such as rhinitis and asthma. The interaction between depression, anxiety, and severity of chronic rhinosinusitis (CRS) has been suggested. We aimed to access the relationship between psychological stress, severity of CRS, and atopy. Sixty-three consecutive patients referred with CRS were asked to score the severity of rhinosinusitis symptoms on a visual analog scale and to fill in questionnaires on the disease-specific quality of life and perceived stress—22-item Sino-Nasal Outcome Test (SNOT-22) and measure of perceived stress (MPS) scale, respectively. Inclusion criteria for the study were a reliable allergy evaluation and a recent computerized tomography (CT) scan of the sinuses. Patients with nasal polyps (NPs), asthma, and previous surgery were excluded. The study group consisted of 14 allergic and 18 nonallergic patients with CRS without NPs (CRSsNPs). Correlation between MPS and SNOT-22 scores in the study group was highly significant (Pearson $r = 0.61$; $p = 0.001$). Patients with higher stress scores had significantly stronger postnasal discharge, thick discharge, cough, disturbed sleep, fatigue, and sadness. Postnasal drip was significantly stronger in patients with allergy. The correlation between SNOT-22 and CT scores was insignificant. The correlation between MPS and SNOT-22 scores suggests an interaction between severity of CRS and chronic stress, but not with the extent of the disease on CT in CRSsNPs. Chronic psychological stress might be one of the factors that modifies the disease severity and may lead to uncontrolled disease in CRS patients.

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Chronic rhinosinusitis (CRS) is a common disorder that has a significant impact on health-related quality of life (HRQL) and its prevalence in the European Union was estimated to be between 7 and 27%.¹ CRS is a recognized risk factor for asthma exacerbations. The adjusted odd ratio for asthma in patients with associated allergic rhinitis and CRS is 11.85.² CRS is defined, according to the European position paper on rhinosinusitis and nasal polyps (EPOS 2012), as a persistence of at least 2 of 4 characteristic symptoms (obstruction, hypersecretion/postnasal drip, headache/facial pressure, and smell impairment), for >12 weeks. The diagnosis should be confirmed by endoscopy and/or imaging.³ However, according to the EPOS document, severity staging is based on symptom scores on the visual analog scale (VAS) and the impact on HRQL, and not on computed tomography (CT) or endoscopy scores. CRS is divided into clinical phenotypes according to endoscopic findings: CRS with nasal polyps (CRSwNPs) and CRS without NPs (CRSsNPs).

Disease-specific questionnaires for CRS, such as the 22-item Sino-Nasal Outcome Test (SNOT-22), reveal significant deterioration in different aspects of HRQL. A strong association between SNOT-22 score and anxiety and depression scores in patients with CRS was shown recently.⁴

Approximately 20% of patients with CRS are not well controlled with recommended treatment. Factors that modify the effectiveness of “adequate” medication to control the disease need to be recognized and, if possible, prevented or eliminated.⁵ Psychosocial stress may be one of these factors. Chronic stress exposure leads to a greater risk of onset and may modify the severity of several atopic respiratory disorders, such as allergic rhinitis and asthma.^{6–8} Posttraumatic stress disorder (PTSD) is associated with worse outcomes in SNOT-22 questionnaire in CRS patients with PTSD compared with CRS patients without PTSD.⁹ Chronic stress modifies innate immune response to infection and may be related to the glucocorticoid receptor resistance.¹⁰ It suggests that chronic stress may affect severity and treatment response in CRS; however, this hypothesis was not evaluated in the literature.

We hypothesized that chronic stress and allergic sensitization affected the symptoms severity and HRQL impairment in CRS patients. To avoid heterogeneity related to different patterns of symptoms in different phenotypes and comorbidities,¹¹ we applied selection criteria. The aim of this study was to evaluate the interaction of chronic psychological stress and severity

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of symptoms, HRQL, and atopic status in patients with CRSsNPs.

MATERIALS AND METHODS

Sixty-three patients referred with CRS, who gave their informed consent to enter the study, were asked to score symptoms severity on a VAS and to fill in questionnaires on the disease-specific HRQL and perceived stress—SNOT-22 and measure of perceived stress (MPS) scale, respectively. They were referred because of persisting symptoms, unresponsive to medical treatment. The study was approved by the Ethics Committee of University Hospital “Sestre milosrdnice,” Zagreb School of Medicine and School of Dentistry.

Inclusion criteria were a reliable allergy evaluation, a recent sinus CT scan, positive endoscopy, and a mean VAS of >3 on two of major CRS symptoms. The patients with CRSwNPs, asthma, previous sinus surgery, aspirin sensitivity, or any acute or systemic disease affecting the airways were excluded. The final study group was 14 allergic and 18 nonallergic patients with CRSsNPs. A group of 10 control subjects (medical staff in the department) who were not diagnosed or treated for CRS were also asked to fill in the SNOT-22 and MPS scale.

The diagnosis and staging of sinus disease were in concordance with EPOS criteria.³ Patients had been treated with nasal steroids and lavages for at least 3 months continuously before inclusion.

Patients filled in VAS, SNOT-22, and MPS scales.¹² Sinus CT scans were scored using Lund–Mackay staging system.¹³ We wanted to test the effect of perceived severity of nasal symptoms on a VAS scale and perceived stress on an MPS scale on HRQL (defined as HQ subscale result on SNOT-22 questionnaire).

The VAS questionnaire was used to evaluate current perception of severity of major symptoms: nasal congestion, runny nose, postnasal secretion, feeling of fullness in the face, facial pain, headache, tearing, coughing, nose bleed, sneezing, and nasal itch.

The SNOT-22 is a validated test based on a self-reporting measure of symptom severity and HRQL in rhinosinusitis. It has 22 questions, where patients rate severity of symptoms or HRQL item impairment on a 6-point Likert-type scale (0–5). In the general population the SNOT-22 score is around 30 points.¹⁴

MPS scale measures emotional, behavioral, and cognitive aspects of distress.¹² Our scale modification consisted of 48 statements with which patients indicated their perceived stress on a 5-point Likert-type scale. The scale was validated in the Croatian language on a sample of 165 healthy adults.¹⁵

The distribution of the data was calculated using the Kolmogorov–Smirnov test. Internal consistency was measured with Cronbach’s α . Statistical analysis was per-

formed depending on the normality of the distribution by the *t*-test, ANOVA and Mann–Whitney *U* two-tailed tests for unpaired comparisons. Two-way ANOVA was conducted to test the effect of perceived severity of nasal symptoms and perceived stress on HRQL.

The Mann–Whitney *U* test was then used for between-group comparison and the correlations with Pearson and Spearman rank correlation test. All conclusions were based on a significance level of $p < 0.05$.

RESULTS

The study sample comprised of 32 participants (11 male and 21 female subjects). There was no difference in the age between the subgroups considering gender and allergy—14 CRSsNP patients with allergic sensitization (27–62 years old; 8 female and 4 male subjects; mean age, 42.4 years) and 18 CRSsNP patients without sensitization (23–65 years old; 11 female and 7 male subjects; mean age, 44.5 years). The control group consisted of 7 female and 3 male subjects (age range, 25–52 years; mean age, 36.5 years). The data distribution was normal. Main results comparing allergic and nonallergic subjects are presented in Table 1. Comparison between the subgroups (allergy, stress, and gender) was performed with nonparametric tests despite the normal data distribution because of small sample size.

Cronbach’s α confirmed high internal consistency of the scales used in the study. The α -coefficients were 0.83, 0.94, and 0.97 for VAS, SNOT-22, and MPS scale, respectively.

Comparing symptom scores between allergic subjects versus nonallergic subjects, the only significant differences were postnasal drip and itch in VAS ($p = 0.025$ and 0.045 , respectively) and postnasal drip in SNOT-22 ($p = 0.006$). In MPS scale allergic subjects rated significantly higher back pain ($p = 0.034$) and startle response ($p = 0.025$).

Comparing symptoms related to gender, several symptoms in VAS scale were significantly higher in female subjects: postnasal drip, facial pain, tearing, and cough. Female subjects rated their perceived stress on the MPS scale significantly higher than male subjects (mean male, 43.45; mean female, 67.38; $p = 0.049$).

Comparing symptoms between the high and low stress subgroups (over and under the median score in MPS), no differences were found in VAS results (the item nasal obstruction was marginally significant: mean no stress (Mns) = 4.0; mean stress (Ms) = 6.0; $Z = 1.92$; $p = 0.055$); but SNOT-22 revealed many differences. The high stress subgroup had a higher total SNOT-22 score (Mns = 31.8; Ms = 52; $Z = 2.59$; $p = 0.01$). The high stress subgroup rated the following CRS symptoms and HRQL items in SNOT-22 significantly higher: cough ($p = 0.037$), postnasal discharge ($p = 0.004$), thick nasal discharge ($p = 0.008$), ear full-

Table 1 VAS scores for main CRS symptoms, SNOT-22 scores (total score, nasal symptoms, and HRQL items separately), and Lund-Mackay CT score for allergic and nonallergic subjects and for the whole study group

Parameter (points)	Allergic <i>n</i> = 14 (mean ± SD)	Nonallergic <i>n</i> = 18 (mean ± SD)	All <i>n</i> = 32 (mean ± SD)
VAS congestion (cm)	6.5 ± 2.44	5.83 ± 0.65	6.13 ± 2.62
VAS runny nose (cm)	6.07 ± 2.75	4.89 ± 2.74	5.41 ± 2.77
VAS postnasal drip (cm)	7.93 ± 2.06**	5.33 ± 3.25	6.47 ± 3.05
VAS facial pain (cm)	2.32 ± 0.62	3.2 ± 0.76	2.41 ± 2.82
VAS smell (cm)	3.64 ± 3.71	3.17 ± 3.34	3.38 ± 3.47
Total SNOT-22 score	48.29 ± 15.01	35.78 ± 24.61	41.25 ± 21.59
SNOT-22 rhino score	28.71 ± 10.05	21.17 ± 13.64	24.47 ± 12.61
SNOT-22 HRQL score	19.57 ± 7.38	14.94 ± 12.07	16.97 ± 10.39
Total MPS score	68.21 ± 36.87	52.11 ± 39.34	58.97 ± 38.48
Lund Mackay CT score	5.7 ± 4.36	6.88 ± 3.46	6.45 ± 4.01

***p* < 0.01 difference between allergic and nonallergic subjects.

VAS = visual analog scale; CRS = chronic rhinosinusitis; SNOT-22 = 22-item Sino-Nasal Outcome Test; HRQL = health-related quality of life; CT = computed tomography; MPS = measure of perceived stress.

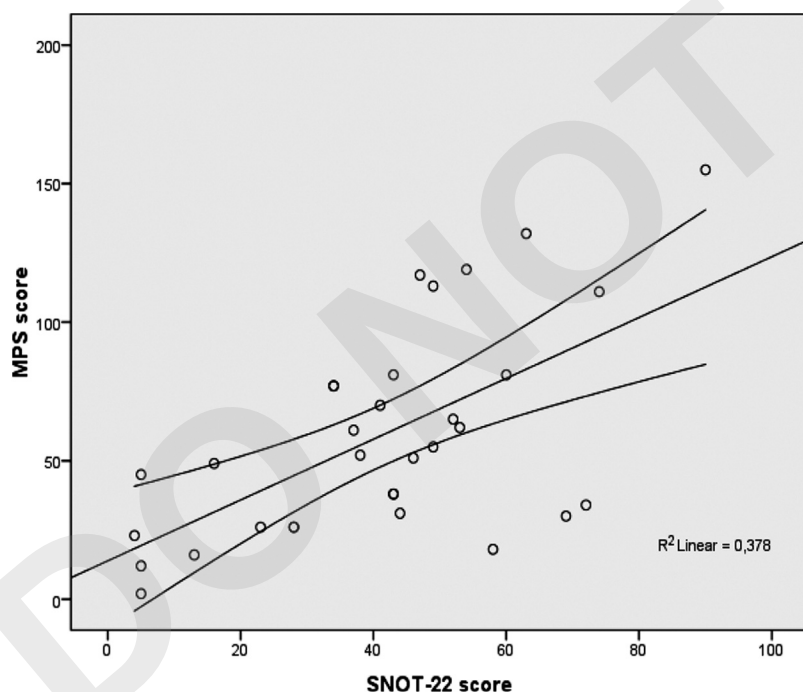


Figure 1. Correlation between MPS and SNOT-22 scores in CRSsNP (allergic + nonallergic). Correlation between MPS and SNOT-22 total scores was highly significant: $r = 0.61$; $p = 0.001$. MPS, measure of perceived stress; SNOT-22, 22-item Sino-Nasal Outcome Test; CRSsNPs, chronic rhinosinusitis without nasal polyps.

ness ($p = 0.027$), dizziness ($p = 0.006$), waking up tired ($p = 0.01$), fatigue ($p = 0.002$), reduced productivity ($p = 0.0001$), and sadness ($p = 0.0001$). The correlation with facial pain in SNOT-22 and MPS was also significant ($r = 0.485$; $p = 0.005$).

The control group had an SNOT-22 range between 2 and 36 points (mean, 15.5 ± 12.78) and MPS scale range between 5 and 82 points (mean, 25.4 ± 22.72).

Correlation between MPS and SNOT-22 total scores was highly significant ($r = 0.61$; $p = 0.001$; Fig. 1). We have also found significant correlations between nose-specific symptom scores in SNOT-22 and MPS ($r =$

0.499 ; $p = 0.009$) and HRQL item scores ($r = 0.678$; $p = 0.0001$), respectively.

Correlation between MPS and SNOT-22 total scores for the whole group of 63 patients was also significant ($p = 0.001$); however, the correlation coefficient was lower (Pearson's $r = 0.446$; Fig. 2.). Correlation between MPS and SNOT-22 was also significant for the control group (Spearman's $\rho = 0.823$; $p = 0.003$).

There was a significant main effect of perceived stress in a two-way ANOVA. Subjects who perceived their stress level higher rated their quality of life worse than subjects who perceived their levels of stress lower

Figure 2. Correlation between MPS and SNOT-22 for all 63 patients (CRSsNPs and CRSwNPs, with and without surgery included). MPS, measure of perceived stress; SNOT-22, 22-item Sino-Nasal Outcome Test; CRSsNPs, chronic rhinosinusitis without nasal polyps; CRSwNPs, chronic rhinosinusitis with nasal polyps.

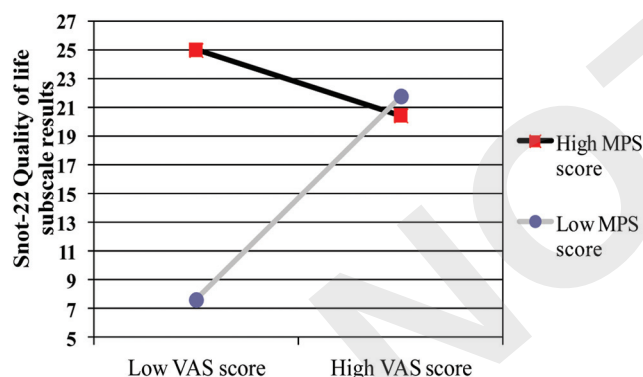
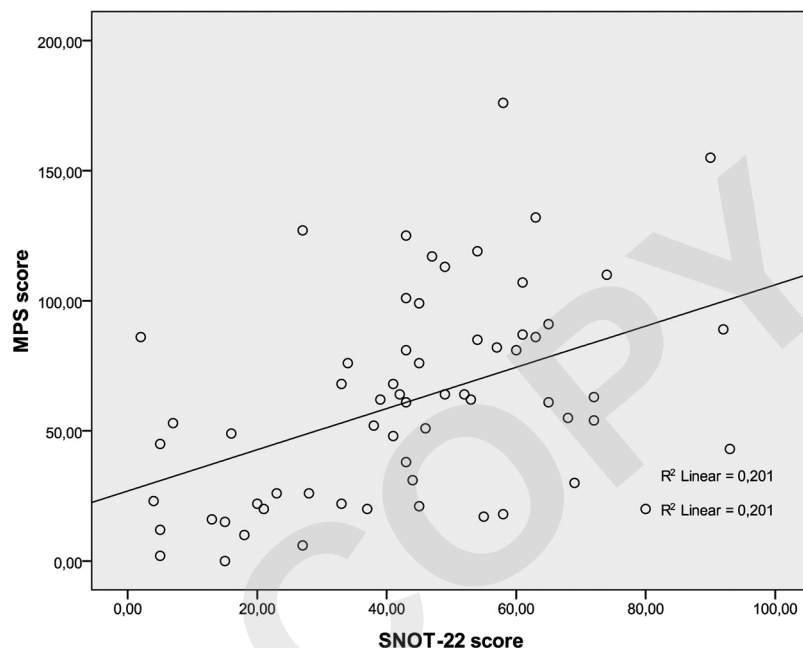


Figure 3. Two-way ANOVA. A significant interaction was found between perceived stress and severity of nasal symptoms on perceived HRQL. In the group of subjects who perceived their stress level lower (below the median on the MPS scale), only those who perceived their nasal symptoms as severe (over the median on VAS scale) rated their HRQL lower, as opposed to highly stressed subjects (above the median on the MPS scale) who rated their HRQL as low regardless of the perceived severity of their nasal symptoms. HRQL, health-related quality of life; VAS, visual analog scale; MPS, measure of perceived stress.

($p = 0.015$; Fig. 3) The main effect of perceived severity of nasal symptoms in VAS was not significant.

The correlation between SNOT-22 score and Lund-Mackay CT score was not significant ($r = 0.06$; $p = 0.77$).

DISCUSSION

This study showed a significant correlation between symptoms severity, HRQL, and perceived stress in patients with CRS. A significant interaction was found between perceived stress and severity of nasal symp-

toms on HRQL. In the group of subjects who perceived their stress level to be lower (below the median on the MPS scale), only those who perceived their nasal symptoms as severe (over the median on VAS scale) rated their HRQL lower, as opposed to highly stressed subjects (above the median on the MPS scale) who rated their HRQL to be low regardless of the perceived severity of their nasal symptoms. Absence of correlation between SNOT-22 and CT scores is in concordance with the literature.³

The limitation to the study is that we have shown a significant correlation between SNOT-22 and MPS scale in the control group of subjects who do not suffer from CRS. The SNOT-22 and MPS scores in the control group were significantly lower than the scores of the study group. The significance of the correlation may be attributed to the similar items in HRQL part of SNOT-22 questionnaire, included also in the MPS scale, such as sleep, fatigue, and depression. On the other hand, we have confirmed our hypothesis that patients with higher scores for perceived stress experience some CRS symptoms as more severe, such as postnasal drip, thick nasal discharge, and cough in SNOT-22 scale and obstruction in the VAS scale.

According to our knowledge, our study is the only one that has separately tested the interaction of perceived stress, severity of symptoms, and HRQL, related to the allergic sensitization. Most of the studies include a heterogeneous group of CRS patients with both phenotypes (CRSsNPs and CRSwNPs), previously operated, regardless of comorbidities. Similar patterns of symptoms may be related to different phenotypes and endotypes within the spectrum of CRS, which may significantly affect the outcomes and the

response to treatment.¹⁶ However, in an attempt to avoid heterogeneity, we may have introduced some drawbacks to this study that might be related to a small study group (caused by more strict selection criteria) and institutional bias (patients refractory to treatment, referred for sinus surgery). Selection of CRSsNP patients as the study group has been based on a significant difference between CRS phenotypes in symptom pattern and CT scores.¹¹ Interestingly, despite significantly worse objective scores (endoscopy and CT), it was shown that CRSwNP patients report significantly better HRQL and less facial pain as measured by VAS scores pre- and postoperatively.¹⁷

In patients with CRS and PTSD 38% of patients chose items that were related to emotional, fatigue, and sleep symptoms as those that mostly affected their lives and only 12% chose items related to the nasal problems alone, and 39% of patients in the CRS group chose as worst items those related to nasal problems.⁷ The total SNOT-22 score of patients from our study falls in the range of CRS without PTSD from the aforementioned study and is much lower than the total SNOT-22 score for the PTSD subgroup.

The other study, which attempted to subclassify CRS into distinct phenotypes and endotypes (according to CT scans, atopy, immune response, and symptoms) noted that there is a subgroup of patients with severe CRS symptoms, with minimal mucosal pathology on CT scans.¹⁸ These patients have shown a high deterioration in HRQL and in 26% of these patients, the criteria for chronic fatigue syndrome were met. An epidemiological overlap between chronic fatigue syndrome, fibromyalgia, PTSD, rhinitis, and CRS has been found. Such disorders may need an active collaboration between allergists, otolaryngologists, rheumatologists, and psychiatrists.¹⁹ High prevalence of fatigue, sleep disorders, and pain syndromes have been recorded among CRSsNP patients in our study group, however, with scores in a lower range than in patients with PTSD or chronic fatigue syndrome. A survey on asthma has shown that perceived stress is a major variable related to HRQL in these patients, and that it correlated with asthma severity.²⁰

Data from the literature have suggested an impact of the attachment anxiety on surgical outcomes in patients with CRS.²¹ However, surgical treatment in CRS has also resulted in the improvement in HRQL, with the major effect achieved on the fatigue reduction.²²

As to the gender difference, acquired results show significantly higher female ratings on many MPS items. Higher female ratings of perceived stress are consistent with those of other studies.^{23–26} In pain report analyses and in experimental pain research,^{27–29} studies of gender differences in pain perception generally confirm higher pain sensitivity in female subjects.

The severity of CRS symptoms in our study group is comparable with those in studies evaluating treatment

outcomes in moderate-to-severe uncontrolled CRS.³⁰ Scores in MPS are similar to values in patients with alopecia areata. Although we could not detect the interaction of perceived stress with individual symptoms of CRS in VAS scales, SNOT-22 items indicated the interaction with a variety of symptoms (postnasal drip, thick discharge, facial pain, and cough). The difference between atopic and nonatopic patients is reflected only in a single symptom—postnasal drip, which is significantly stronger in the atopic ones. Total SNOT-22 score is insignificantly, but markedly higher in atopic patients (mean, 35.78 versus 48.29, respectively), suggesting further research on a greater study group. According to the EPOS guidelines, only severe CRS, refractory to medical treatment (glucocorticoids), is an indication for surgical management. Perceived stress should be considered as one of the CRS severity modifiers. Worse patient-reported disease severity, as measured by the SNOT-22, was significantly associated with the treatment choice for CRS.³¹ Depression and anxiety have been significantly correlated with HRQL items in SNOT-22, but only depression was related to nose-specific symptoms.⁴ CRS patients with depression have lower HRQL before surgery but show similar improvement rate after surgery as CRS patients without depression.^{32,33} Olfactory dysfunction has recently been recognized as one of the CRS symptoms contributing to anxiety and depression.³⁴ Olfaction scores in our study group (CRSwNPs and asthmatic patients excluded) correlated significantly with some of the nose-related symptoms and SNOT-22 items, but they were not correlated with perceived stress. However, beneficial effect of sinus surgery on fatigue²² and depression³³ has not been tested in randomized trials, and the placebo effect of surgery may also be considered. Hypothetically, chronic stress may induce glucocorticoid receptor resistance¹⁰ and unresponsiveness to standard CRS treatment, resulting in (maybe) unnecessary surgery. The hypothesis that psychological stress-induced steroid resistance may play a role in the unresponsiveness to inhaled steroid treatment in asthma has already been suggested.³⁵

There is no doubt that CRS is a significant burden (economic and HRQL), due to increased odds ratios for activity, work, and social limitations.³⁶ Perceived stress should be recognized as a disease severity modifier, which may lead to uncontrolled disease and increase the burden.

CONCLUSION

Our results indicate interaction between psychological stress and subjective severity of CRS. Patients with allergic sensitization and female patients tended to have higher scores for some of the symptoms of and stress-related items, but only a few reached statistical

significance. Subjective symptoms and the reduction in HRQL did not correlate with the disease extent on CT scans. Additional research on a larger sample, with a follow-up after treatment, might show whether perceived stress could be one of the factors contributing to poor control of CRS.

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