

Co-morbid anxiety and depression impacts on the correlation between symptom and radiological severity in patients with chronic rhinosinusitis*

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Abstract

Background: Previous studies have reported that there is little correlation between sino-nasal outcome test (SNOT-22) score in chronic rhinosinusitis (CRS) and objective radiological scoring, although conclusions vary. We aimed to investigate whether comorbid anxiety and depression, which are highly prevalent in patients with CRS may cause symptom amplification and account for the lack of correlation in previous studies.

Methodology: 100 patients with CRS were evaluated using the General Anxiety Disorder-7 (GAD-7), Patient Health Questionnaire-9 (PHQ-9) and SNOT-22 questionnaires as well as the Lund Mackay Score (LMS).

Results: Overall correlation analysis did not show a significant relationship between SNOT-22 and LMS scores. Subgroup analysis of patients who do not suffer with anxiety and depression showed a significant correlation between SNOT-22 and LMS scores. The nasal domain of the SNOT-22 showed strongest correlation to LMS in this patient group. We also observed a significant difference in both median SNOT-22 and LMS between patients who suffered both anxiety and depression and patients without either comorbidity.

Conclusion: When CRS patients who do not have anxiety and depression are analysed in isolation, or when these conditions are controlled in a multivariable regression, there is a significant correlation between radiological findings and symptom score. This correlation is absent in patients with co-morbid anxiety and depression. Anxiety and depression should be considered in patients in whom there is a mismatch in symptom and radiological disease severity as it is associated with symptom amplification.

Key words: rhinosinusitis, anxiety, depression, Lund-Mackay score, SNOT-22

Introduction

Rhinosinusitis can be defined as inflammation of the mucosal lining involving the nose and paranasal sinuses⁽¹⁾, and when symptoms persist for longer than 12 weeks it is categorised as chronic. Chronic rhinosinusitis (CRS) is a highly prevalent disease affecting around 10% of the adult population in the United Kingdom⁽¹⁾. CRS is associated with significant healthcare costs, reduced quality of life (QOL) and absenteeism^(2,3). A large group of patients suffer from recurrent or persistent symptoms despite optimum medical treatment and surgical intervention. In patients who suffer with CRS, there is evidence that the seve-

riety of their reported symptoms is impacted by patient-specific factors such as age, gender, tobacco use, mental and physical co-morbidities⁽⁴⁻⁶⁾. These factors may also influence patient's perceived benefit from surgical management. There is also evidence that comorbid anxiety and depression may impact reported symptom severity^(4,7,8). Depression and anxiety are the two most predominant mental health conditions worldwide⁽⁹⁾. The Office of National Statistics reports that 19.1% of adults in the UK showed symptoms of anxiety or depression⁽¹⁰⁾. In the US, depression is a leading cause of disability and its economic burden is estimated to be around

\$83 billion annually⁽¹¹⁾. There is also evidence that the rate of anxiety and depression is higher in those who suffer from CRS^(4,7,8) with the estimated prevalence of depression in CRS patients is between 20-36%⁽¹¹⁻¹³⁾.

A number of previous studies exploring the correlation between CRS symptomatology and radiological scoring have concluded that there is little correlation^(14,15). We hypothesize that the lack of correlation found may be due to the modification of symptom severity by patient factors such as co-existing anxiety and depression. This study aims to evaluate whether the correlation between sino-nasal outcome test (SNOT-22) scores and the radiological severity of disease, measured by the Lund Mackay CT scores (LMS) of CRS patients is changed by the presence of comorbid anxiety and depression and compare them to the scores in those who do not suffer from either anxiety or depression.

Materials and methods

Patient group

In this study, 100 consecutive patients referred to rhinology outpatient department at Guy's hospital with CRS (diagnosed according to the EP3OS criteria) were invited to participate. From 8th October to 2018 to 7th June 2019, patients completed validated questionnaires including SNOT-22, General Anxiety Disorder-7 (GAD-7) and Patient Health Questionnaire-9 (PHQ-9). Diagnostic endoscopy was performed on each patient by a senior registrar or consultant. Prospective evaluation of computed tomography (CT) imaging with Lund Mackay scoring was used for assessment of the severity of the CRS.

SNOT-22 questionnaire

The SNOT-22 is a validated patient-reported outcome measure, with 22 items, each scored using a Likert scale from 0 – 5. The total score ranges from 0-110, with higher scores representing greater symptom severity. Among people without CRS, SNOT-22 score up to 7 is considered as normal⁽¹⁶⁾. It is organised into 5 domains: rhinologic, extra-nasal rhinologic, ear/facial, psychological and sleep. When compared to other patient-reported outcome measures, SNOT-22 has the highest psychometric properties and quality of development methodology as well as being the most widely used tool^(17,18). Moreover, recent advances in technology enabled severity of disease to be screened using the mobile phone application⁽¹⁹⁾.

GAD-7

GAD-7 consists of seven questions based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for General Anxiety Disorder (GAD). The patient is asked to score their symptoms from 0-3 during the last two weeks⁽²⁰⁾. The scores range from 0-27, with a higher score GAD-7 was originally validated in a primary care setting, with a diagnostic score of 10 giving a sensitivity of 0.89 and a specificity value of

Table 1. Characteristics of 100 respondents.

	Total (n=100)
Gender (M:F, %)	58:42 (58:42)
Age (mean (SD))	45.38 (13.38)
CRSwNP:CRSnNP (%)	76:24 (76:24)
Smoking (%)	9 (9)
Asthma (%)	20 (20)
Anxiety (%)	14 (14)
Depression (%)	27 (14)
Anxiety and depression (%)	14 (14)

0.8221. Furthermore, a more recent systemic review has shown cut off scores from 7-10 have similar sensitivity and specificity⁽²²⁾. A cut off of 10 was used as diagnostic of anxiety in this study.

PHQ-9

The PHQ-9 is a 9 item questionnaire based on the DSM-IV diagnostic criteria for depression. Patients answer questions based on frequency of symptoms over the past two weeks⁽²³⁾. The PHQ-9 score can range from 0-27, as each of the items can be scored from 0 (not at all) to 3 (nearly every day). The PHQ-9 is scored using simple addition with a cut-off of 10 having a sensitivity of 88% and a specificity of 88%⁽²⁴⁾. A score of 10 or greater was used in this study as diagnostic of depression.

Lund Mackay score

The Lund-Mackay score grades the extent of opacification of each of the major sinus groups on CT and obstruction of the ostiomeatal complex, with a total score ranging from 0 (complete lucency of all sinuses) to 24 (complete opacity of all sinuses). A cut-off of 4, corresponding to the mean LMS in a healthy population, has been proposed for patients undergoing endoscopic sinus surgery^(25,26).

Statistical analysis

The one-sample Kolmogorov-Smirnov test was used to test for normal distribution amongst the continuous data sets. The p-value showed statistical significance and therefore the continuous data sets were not normally distributed. The quantitative data were expressed as means, standard deviations and medians and ranges.

Non-parametric Spearman's rank correlation coefficient was used to test for association between PHQ-9, GAD-7, LMS, SNOT-22 as well as the domains of the SNOT-22 (nasal, extra-nasal, ear/facial, psychological dysfunction and sleep dysfunction). This was done using the group as a whole (n=100) and also when the cohort was dichotomised into patients that suffer from anxiety and/or depression using GAD-7 and PHQ-9 scores of greater

Table 2. SNOT-22, LMS, GAD-7 and PHQ-9 results in overall cohort, patients with anxiety and depression and in patients with neither of those.

	Total (n=100)		NAD (n=73)		AD (n=14)	
	Mean (SD)	Median (range)	Mean (SD)	Median (range)	Mean (SD)	Median (range)
SNOT-22	43.16 (27.65)	42 (0-105)	33.11 (21.16)	34.00 (0-82)*	66.5 (28.49)	76.00 (1-96)
LMS	11.67 (6.24)	11 (0-24)	11.85 (5.84)	11.00 (0-23)*	7.93 (5.55)	6.50 (0-20)
GAD-7	3.13 (5.79)	0 (0-21)	0.68 (1.34)	0 (0-9)	16.64 (2.82)	17.00 (11-21)
PHQ-9	4.94 (7.56)	1 (0-27)	0.67 (1.44)	0 (0-9)	18.14 (5.26)	17.50 (11-27)

* significant compared to AD (Mann Whitney U test). NAD = Neither anxiety nor depression, AD = Anxiety and depression.

than 10 (n=14) and those who suffer with neither (n=73). Median scores of SNOT-22 and LMS between those who suffer with anxiety and depression and those who do not were compared using The Mann-Whitney U test. Multivariate linear regression was also used to test for association between PHQ-9, GAD-7, LMS and SNOT-22 in the two groups.

Results

A total of 100 patients with CRS were included in our study, consisting of 58 men and 42 women with mean age 45.38 ± 13.38 years (range, 19 to 74 years). Other respondents' characteristics are shown in Table 1. Of the 100 patients included, mean PHQ9 score was 4.94 (SD=7.56), mean Gad-7 score was 3.13 (SD=5.79). Mean total SNOT-22 score was 43.16 (SD= 27.65). Overall mean LMS was 11.67 (SD=6.24) (Table 2).

Prevalence of depression and anxiety in patients with CRS

In our cohort, the prevalence of anxiety was 14% (n=14) using a cut-off Gad-7 score ≥ 10 . 27 (27%) patients met the cut off for depression using a cut-off PHQ-9 score ≥ 10 . Among the 27 patients screening positive for depression, 35.1% had no reported history of depression or psychiatric history. Two patients (2%) reported a history of another psychiatric illness (schizophrenia, anxiety). Interestingly, all 14 (14%) patients with Gad-7 score ≥ 10 had also PHQ-9 score ≥ 10 . In our group, 73% (n=73) patients scored below cut-offs for both anxiety and depression.

SNOT-22 and LMS in patients with anxiety and depression vs no anxiety and depression

Among patients with both depression and anxiety (n=14), median SNOT-22 score was 76 (range=1-96) and median LMS score was 6,5 (range=0-20). In patients who had neither anxiety nor depression (n=73), the median SNOT-22 score was 34 (range=0-82) and median LMS score was 11 (range=0-23). We observed a significant difference in both median SNOT-22 ($p < 0.0001$) and LMS ($p = 0.023$) between patients who suffered both anxiety and depression and patients who reported neither of them using the Mann Whitney U test. Those with anxiety and

depression had significantly higher SNOT-22 scores while those without had higher LMS.

Correlation between GAD-7, PHQ-9, SNOT-22 and LMS

Subsequently, using Spearman's rank correlation, we evaluated whether there is an association between SNOT-22 scores and the Gad-7 and PHQ-9 scores across all patients. There was a statistically significant association between total SNOT-22 and both Gad-7 and PHQ-9 scores ($q = 0.49$, $p < 0.0001$ and $q = 0.64$, $p < 0.0001$, respectively), with higher SNOT-22 scores reported in patients with both higher GAD-7 and PHQ-9 scores.

Across all patients, using pairwise comparisons we did not observe a significant correlation between LMS and either the SNOT-22, PHQ-9 or Gad-7 scores, using Spearman's rank correlation. In patients with neither depression or anxiety, there was a positive statistically significant correlation between radiological findings using LMS and symptom severity using SNOT-22 scores ($q = 0.309$, $p = 0.008$). In patients with anxiety and depression, there was no significant correlation between LMS and SNOT-22. However, there was significant correlation between SNOT-22 and PHQ-9 ($\rho = 0.590$, $p = 0.026$).

We then performed a multivariate linear regression to predict LMS from gender, age, smoking status, asthma status, Gad-7, PHQ9 and SNOT-22 score. LMS statistically significantly predicted SNOT-22, $F(1, 54) = 3.948$, $p = 0.001$, $R^2 = 0.353$, when anxiety and depression scores were controlled for in the regression model (Figure 1).

When breaking down the SNOT-22 into its domains, there was significant correlation between the nasal domain and LMS ($\rho = 0.348$, $p = 0.003$). A weak correlation was also found between LMS and the ear/facial pain domain and the sleep dysfunction domain (Table 3).

Discussion

Depression is a common medical illness that negatively affects how one feels, thinks and acts. Depression causes feelings of sadness and/or a loss of interest in activities once enjoyed. It can lead to a variety of emotional and physical problems and can

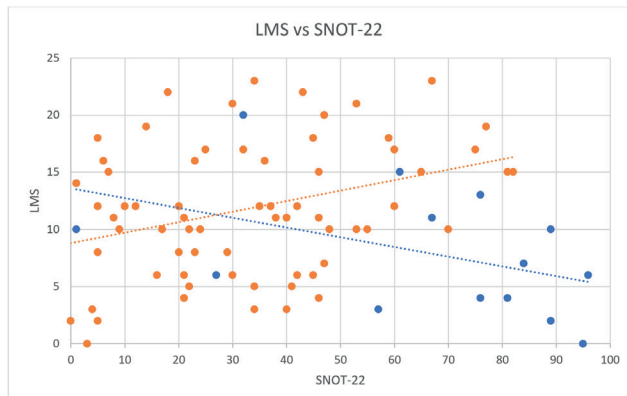


Figure 1. Linear relationship between LMS and SNOT-22 in patients who suffer with both anxiety and depression. Orange = Neither anxiety nor depression, Blue = Anxiety and depression.

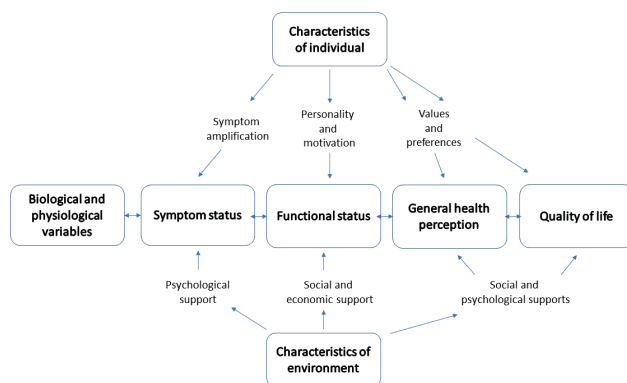


Figure 2. Relationships between physiologic variables of disease and patients' symptoms.

decrease a person's ability to function at work and at home. For example, depression can be triggered from the loss of a spouse through divorce, or the perception that such a loss is imminent⁽²⁷⁾. Anxiety is an emotion characterised by an unpleasant state of inner turmoil, often accompanied by nervous behaviour such as pacing back and forth, somatic complaints, and rumination. It is the subjectively unpleasant feelings of dread over anticipated events^(28,29).

A cohort study of 48,672 patients over 11 year shows depression rates to be 1.51-fold higher in those with CRS⁽⁵⁾. A meta-analysis has shown that depression is commonly associated with CRS but is likely under-diagnosed in many patients⁽¹³⁾. The combination of anxiety and depression in patients with CRS has been shown to increase the burden on healthcare, with poorer perceived outcomes after treatment and increased utilisation of resources including primary care visits and antibiotic usage⁽¹⁰⁾.

14% (n=14) of patients included in the study scored 10 or more on the GAD-7 questionnaire, a score highly predictive of clinically significant anxiety. 27% (n=27) had a PHQ-9 score of greater than 10 which is also highly predictive of depression. A depression rate of 27% in CRS is similar to that found in previous

Table 3. Spearman's correlation analysis between SNOT-22 and LMS in patients without anxiety and depression.

	NAD (n=73)	
	ρ	p
Nasal	0.348	0.003**
Extra-Nasal	0.078	0.510
Ear/Facial	0.29	0.013*
Psychological	0.200	0.090
Sleep Dysfunction	0.243	0.038*

**Correlation is significant at the 0.01 level (2-tailed). *Correlation is significant at the 0.05 level (2-tailed).

studies⁽¹¹⁻¹³⁾ and higher than the prevalence in the general population of the UK⁽³⁰⁾. Over a third of patients who scored 10 or more on the PHQ-9 questionnaire did not have previously diagnosed depression, which fits with previous studies regarding the under-diagnosis of depression in CRS⁽¹³⁾. Patient's total scores from the questionnaires were conveyed to their GP via a letter. In our study, SNOT-22 scores were significantly higher in patients with anxiety and depression over those who do not have either, despite significantly lower radiological burden of disease. This differs from some previous studies that have found no significant difference between anxiety and depression and healthy patients using objective scoring systems^(7,12,31). Our results, however, are similar to those of Smith et al. who divided patients into different sub-groups depending on their co-morbidities. They found depressed patients had the least severe CRS using Lund-Mackay staging as an objective outcome measure⁽³¹⁾. If patients with anxiety and depression experience symptom amplification, they will report higher levels of symptoms and are more likely to be referred from primary care with a lower burden of disease radiologically. Those without anxiety and depression tend to have lower SNOT-22 scores at the same stage of radiological disease severity, and based on symptomatology may be less likely to be referred and only see specialist care once their objective CRS is worse. How mental health illnesses and other co-morbidities interact and affect chronic illnesses such as CRS is subject to debate. As discussed, a number of patient and environmental factors, including a patient's mental health or acute psychological stress, can impact on symptom perception in CRS (Figure 2). However, there is also evidence that depression and anxiety can directly alter the pathophysiology of disease states. Activation of the paraventricular nucleus in depression directly alters the hypothalamic-pituitary adrenal axis and leads to the pro-inflammatory response, including raised cytokines, chemokines and acute phase proteins^(32,33). In patients with anxiety and depression, brain PET scan imaging has revealed

significantly altered neurotransmission in the anterior cingulate cortex⁽³⁴⁾, the area of the brain associated with pain and mood. The overall cause and effect between depression and chronic diseases such as CRS is complex may not be one-directional. There is evidence that CRS predisposes to higher rates of anxiety and depression, while anxiety and depression may also directly affect patients suffering with CRS. Interestingly, this study found a correlation between SNOT-22 and PHQ-9 in the group when analysed as a whole and also when splitting into healthy and those with anxiety and depression.

It is generally accepted that symptom scores for CRS using patient-reported outcome measures such as SNOT-22 have low levels of correlation with objective measures of disease severity such as CT imaging or nasal endoscopic scoring^(14,15). Previous studies have found a mix of results. Some have found a correlation between SNOT-22 and CT scoring while others have found no significant correlation⁽³⁵⁻³⁷⁾. As alluded to above, this discrepancy may in part be due to the influence of co-morbidities such as anxiety and depression. When analysing the whole group in this study, we found no correlation between SNOT-22 and Lund-Mackay staging scores. However, when the groups are broken down into those who suffer with anxiety and depression and those who do not, the results differ greatly. Patients who suffer with anxiety and depression have no correlation between symptom scoring and objective measures on CT imaging. However, in patients who do not suffer from anxiety or depression, there is strong correlation between SNOT-22 and Lund-Mackay stage scoring. Despite it being generally accepted that anxiety and depression affect symptom scoring, none of the previous studies looking at correlation between symptom and radiological burden have divided the sample into these sub-categories for analysis, or looked at the proportion of patients with underlying anxiety and depression. This may be a contributing factor as to why the correlation between CT scoring and patient-reported

outcome measures has been so varied in the past.

Our results also suggest that when there is a mismatch between symptom and radiological disease severity, it is worth considering if symptom severity may be modified by other factors, such as anxiety and depression, which as shown in this study is commonly underdiagnosed.

As has previously been shown, the SNOT-22 nasal domain showed the strongest correlation to LMS and it is also important to pay close attention to these subsets of questions^(36,37).

Conclusion

The correlation between symptoms and radiological disease severity has been extensively studied and mixed results have been reported in the literature. We have found that comorbid anxiety and depression, which are highly prevalent in patients with CRS may cause symptom amplification and account for the lack of correlation in previous studies. When CRS patients who do not have anxiety and depression are analysed in isolation, or when these conditions are controlled in a multivariable regression, there is a strong correlation. Anxiety and depression should be considered in patients in whom there is a mismatch in symptom and radiological disease severity.

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Authorship contribution

PS and CH: conception and design of the paper. Data Collection: DR, CH, AT, MA and NA. Data analysis: PS and DR. DR: drafting of manuscript. All involved authors have commented and reviewed the paper.

Conflict of interest

The authors declare that they have no conflict of interest.

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