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ORIGINAL RESEARCH

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Association of cough with asthma in chronic rhinosinusitis patients

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Abstract

Objective: To determine whether the complaint of cough in chronic rhinosinusitis (CRS) patients is associated with asthma and if there is a potential predictive value for asthma diagnosis.

Method: Consecutive patients presenting for initial evaluation at a tertiary rhinology clinic who were diagnosed with CRS were considered for inclusion in a cross-sectional study. The presence and severity of cough was determined using the 22-item Sinonasal Outcome Test (SNOT-22). Subgroup analysis included asthma diagnosis confirmed by pulmonary function testing (PFT) in our institution, and for chronic rhinosinusitis patients with (CRSwNP) and without nasal polyps (CRSsNP).

Results: The total study population included 297 patients with a diagnosis of CRS, with 63.9% of patients reporting cough. Physician-confirmed diagnosis of asthma was made in 38.7% of patients, and confirmed in 69.6% by PFT. Cough was more frequently reported by CRS patients diagnosed with asthma (relative risk [RR] = 1.60, 95% confidence interval [CI], 1.13-2.25), with sensitivity of 73.9% (95% CI, 65.0%-81.1%). This remained significant in the CRSsNP subgroup (RR = 2.65, 95% CI, 1.32-5.30), with sensitivity of 83.3% (95% CI, 70.4%-91.3%) and specificity of 41.2% (95% CI, 33.2%-49.8%). Cough was not associated with asthma in CRSwNP patients (RR = 1.26, 95% CI, 0.89-1.79). Cough severity had poor predication for asthma diagnosis (AUC = 0.60, 95% CI, 0.54-0.65).

Conclusions: Complaint of cough is associated with diagnosis of asthma in CRS patients. In CRSsNP, complaint of cough was sensitive for asthma diagnosis, although specificity was low. Cough in CRS patients can be multifactorial and asthma may be an important diagnostic consideration.

Level of evidence: 4.

KEYWORDS

asthma, chronic rhinosinusitis, cough, nasal polyps, SNOT-22

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1 | INTRODUCTION

Asthma is a well-known comorbidity of patients with chronic rhinosinusitis (CRS).[1-4] Various mechanisms have been proposed for linking CRS and asthma in a unified airway model.[2,3,5] CRS severity is also impacted by concomitant asthma,[6,7] and treatment for CRS may improve asthma control.[8-10] Therefore, diagnosis of asthma has important prognostic and management implications for the otolaryngologist treating CRS.

Cough is the most common presenting symptom to ambulatory medical practices, accounting for 3.1% of visits and $3.6 billion in over-the-counter medication sales.[11] Postnasal drainage, asthma, and gastroesophageal reflux disease (GERD) or laryngopharyngeal reflux (LPR) are most often thought to be the source of chronic cough in adults, and are estimated to account for 86% of these patients.[12] These conditions account for up to 99% of chronic cough when abnormal chest X-ray, angiotensin converting enzyme (ACE) inhibitor use, immunocompromised status, and smoking are excluded.[12,13] Cough is a common complaint for CRS patients, and discerning whether this is attributable to local otolaryngic sequela from CRS, comorbid asthma, or other etiologic factors can be difficult. There is also the potential for missed diagnosis in patients without classic symptoms of asthma, as cough might be directly ascribed to CRS, postnasal drainage, GERD, or psychosocial causes.

The 22-item Sinonasal Outcome Test (SNOT-22) is a validated instrument, which has been widely used as a patient reported outcome measure in CRS.[14,15] A response item for cough is included in the SNOT-22 questionnaire and has been found to be internally consistent, although this item is not independently validated for reporting cough severity or health related quality of life (HRQOL) effects.[14] Subsequently, factor analysis has been performed identifying subdomains within the SNOT-22 instrument.[16-18] Cough has been inconsistently assigned to either a "nasal" or "extranasal" subdomain,[16-18] and this may be indicative of a differing response to treatment or impact of comorbidities compared to symptoms more consistently characterized as "nasal."

This study sought to determine if SNOT-22 item response for cough by CRS patients is associated with asthma diagnosis. Asthma is a well described comorbidity of CRS with important prognostic and treatment implications. The SNOT-22 cough item also represents a prospectively collected Likert-type question for analysis of a predictive threshold. These analyses might identify a group of CRS patients that would benefit from additional evaluation for asthma, and a predictive SNOT-22 item score threshold.

2 | MATERIALS AND METHODS

Patients at their initial presentation to the senior author's (DL) rhinology practice between July 1, 2011 and December 31, 2016 were considered for study inclusion. Diagnosis of CRS in accordance with the American Academy of Otolaryngology clinical practice guideline on adult sinusitis[19] was also an inclusion criterion. SNOT-22 questionnaires were prospectively collected from patients at the initial visit. Patients with a history of prior endoscopic sinus surgery (ESS) were excluded to reduce potential confounding of surgery on patient reported symptoms. A previous or subsequent (through January 31, 2018) diagnosis of granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, cystic fibrosis, and invasive fungal sinusitis were exclusion criteria. Prescription for an ACE inhibitor predating the initial rhinology consultation was an exclusion criterion. Patients who did not complete a SNOT-22 questionnaire at the initial visit were also excluded.

The medical record was reviewed to assign the primary diagnosis, according to CRS phenotype, of chronic rhinosinusitis without nasal polyps (CRSsNP) or with nasal polyps (CRSwNP). A diagnosis of comorbid asthma was also recorded from the medical record, as determined by the patient's treating primary care, pulmonary, or allergy/immunology physician. A subgroup analysis was also performed for patients with a diagnosis of asthma confirmed by pulmonary function testing (PFT) performed in our institution. PFT included spirometry, post-bronchodilator testing, and exhaled nitric oxide test. The presence and severity of patient reported cough was made from the related item of the SNOT-22 questionnaire. Response of "1" or greater to this item was recorded as the presence of cough. Among all patients with CRS, complaint of cough was compared in patients with and without asthma by calculating the relative risk (RR) with 95% confidence intervals (CI). Sensitivity and specificity of cough for comorbid asthma was also calculated for significant associations. Subgroup analysis was then performed according to CRS phenotype. SNOT-22 cough item response was assessed as a predictor for comorbid asthma using receiver operating characteristic (ROC) and area under the curve (AUC). The RR of complaint of postnasal drainage and cough were calculated among patients with and without asthma. Multivariable logistic regression with adjusted odds ratios (aOR) was used to analyze the association of both postnasal drainage complaint and asthma diagnosis with cough. Statistical analysis was performed using JMP Pro, Version 14.1.0 (SAS Institute Inc., Cary, North Carolina). The study was approved by the institutional review board of the Mayo Clinic, Phoenix, Arizona.

3 | RESULTS

A total of 297 patients met the study inclusion and exclusion criteria. Asthma was diagnosed in 115 patients (38.7%), whereas 190 patients (63.9%) had complaint of cough. Asthma diagnosis was confirmed in 80 patients (69.6%) by PFT performed at our institution. CRSsNP was the primary diagnosis in 179 patients (60.3%), and CRSwNP was the primary diagnosis in 118 patients (39.7%). Diagnosis of asthma was made in 26.8% of CRSsNP patients and 56.8% of CRSwNP patients, whereas cough was reported in 61.9% and 65.4% of CRsNP and CRSwNP patients, respectively. The mean total SNOT-22 score in the study population was 41.3 (CI, 38.7-43.8), with the mean item response for cough of 1.5 (95% CI, 1.4-1.7). The median cough item response was 1, with an interquartile range of 0 to 3. The complete

TABLE 1 Demographic and clinical characteristics of study population

Characteristic	Number or mean (% or 95% CI)
Age (years)	53.5 (51.6-55.4)
Male	157 (52.9%)
Female	140 (47.1%)
CRSsNP	179 (60.3%)
CRSwNP	118 (39.7%)
Asthma	115 (38.7%)
Allergic rhinitis	64 (21.5%)
Cough	190 (63.9%)
Postnasal drainage	248 (83.5%)
Total SNOT-22	41.2 (38.7-43.8)
SNOT-22 cough item response	1.5 (1.4-1.7)
Lund-MacKay CT score	11.2 (10.4-11.9)

Abbreviations: CI, confidence interval; CRSsNP, chronic rhinosinusitis patients without nasal polyps; CRSwNP, chronic rhinosinusitis patients with nasal polyps; CT, computed tomography; SNOT-22, 22-item Sinonasal Outcome Test.

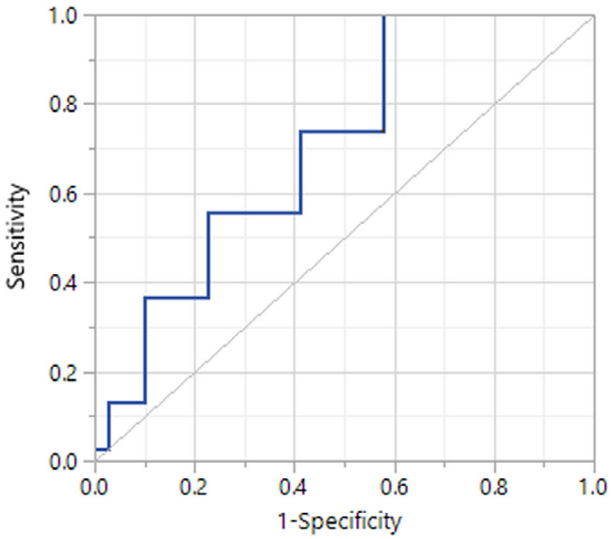

FIGURE 1 Receiver operator characteristic curve for SNOT-22 cough item response as a predictor for asthma diagnosis. Area under the curve = 0.60. SNOT-22, 22-item Sinonasal Outcome Test

demographic and clinical characteristics of the study population are shown in Table 1.

ROC analysis of SNOT-22 item response for cough as a predictor of comorbid asthma was significant, although discriminative ability was poor (AUC = 0.60, 95% CI, 0.54-0.65, Figure 1). The optimal cut-off point corresponded to a cough item response of "1." Positive patient response for cough was associated with a diagnosis of asthma (RR = 1.60, 95% CI, 1.13-2.25, Table 2). This was also significant in the subgroup of patients with CRSsNP (RR = 2.65, 95% CI, 1.32-5.30), but not among CRSwNP patients (RR = 1.26, 95% CI, 0.89-1.79, Table 2). Nasal polyps, however, were associated with diagnosis of asthma independent of cough (RR = 2.12, 95% CI, 1.59-2.82). Among all CRS patients sensitivity of cough for asthma diagnosis was 73.9% (95% CI, 65.0%-81.1%), whereas specificity was 42.3% (95% CI, 35.4%-49.6%). In the CRSsNP subgroup sensitivity was 83.3% (95% CI, 70.4%-91.3%), whereas specificity was 41.2% (95% CI, 33.2%-49.8%).

In subgroup analysis restricting asthma diagnosis to those patients confirmed by PFT in our institution, complaint of cough remained associated with asthma (RR = 1.96, 95% CI, 1.24-3.10). ROC analysis of SNOT-22 cough item response was also statistically significant, but with poor discriminative ability (AUC = –0.62, 95% CI, 0.56-0.68). The optimal cut-off point continued to be an item response of "1" in this subgroup analysis. In CRSsNP patients cough complaint was associated with asthma (RR = 4.93, 95% CI, 1.56-15.55), but this was not significant in the CRSwNP population (RR = 1.41, 95% CI, 0.90-2.21). Using Spearman rho, cough item response was not correlated with spirometry (rho = –0.079, P = .596), post-bronchodilator testing (rho = 0.059, P = .767), or exhaled nitric oxide (rho = –0.066, P = .602).

Asthma patients did not have a significant association between cough and postnasal drainage complaints (RR = 1.23, 95% CI, 0.79-1.91). In contrast, when all patients in the study were considered

TABLE 2 Contingency tables of cough complaint and asthma for all patients, CRSsNP patients, and CRSwNP patients

Patient groups	Asthma	No asthma	RR (95% CI)
All patients with cough	85	105	1.60 (1.13-2.25)
All patients without cough	30	77	
CRSsNP patients with cough	40	77	2.65 (1.32-5.30)
CRSsNP patients without cough	8	54	
CRSwNP patients with cough	45	28	1.26 (0.89-1.79)
CRSwNP patients without cough	22	23	

Abbreviations: CI, confidence interval; CRSsNP, chronic rhinosinusitis patients without nasal polyps; CRSwNP, chronic rhinosinusitis patients with nasal polyps; RR, relative risk.

postnasal drainage was reported by 83.5% of patients, and this was associated with concurrent complaint of cough (RR = 1.59, 95% CI, 1.14-2.22). Among the patients without a diagnosis of asthma this association remained significant (RR = 1.74, 95% CI, 1.11-2.74). Multivariable logistic regression was significant for association of both postnasal drainage (aOR = 2.81, 95% CI, 1.46-5.42) and asthma (aOR = 2.44, 95% CI, 1.32-4.50) with cough.

4 | DISCUSSION

Cough is a common symptom in CRS. Patients and some physicians may attribute cough to be a consequence of sinus disease such as

postnasal or sinus drainage; however, cough is also a common symptom in asthma. Asthma is an important comorbidity of CRS, which impacts disease severity[6,7] and treatment.[8-10] The order in and degree to which underlying potential causes for cough should be pursued remains unclear.[11,20,21] Published guidelines from the American College of Chest Physicians on the diagnosis and treatment of chronic cough recommend an integrative approach considering "upper airway cough syndrome" (UACS), asthma, and GERD.[22,23] These guidelines, however, do not define a clear pathway for diagnosing alternate and multifactorial sources of cough in CRS patients.[22,23] Given that asthma is frequently prevalent in CRS patients and has prognostic and management implications, understanding the relationship of cough with asthma in CRS patients may offer insight on the diagnosis of this symptom.

Among CRS patients undergoing initial evaluation in a rhinology clinic, the complaint of cough is associated with diagnosis of comorbid asthma. Sensitivity for asthma diagnosis is good, particularly among patients with CRSsNP, whereas specificity is poor. The relatively good sensitivity may indicate that CRS patients with cough would benefit from additional evaluation for asthma, whereas poor specificity likely reflects the multiple etiologies for cough. The association remains significant in CRSsNP patients with sensitivity of 83.3%, and could be particularly useful given the lower prevalence of asthma in this group. Conversely, cough was not associated with asthma in CRSwNP patients, and this may be related to the higher prevalence. Nasal polyps were separately associated with asthma, independent of cough. ROC analysis of SNOT-22 item response for cough as a predictor of asthma diagnosis suggests an optimal cutoff value of "1," and discriminative ability is poor as measured by AUC. Therefore, a SNOT-22 item response threshold above "1" does not appear to add diagnostic utility.

Postnasal drainage, as captured in the SNOT-22 questionnaire, was also associated with cough, however this did not remain significant in the group of patients with asthma. On one hand, this is consistent with guidelines and reports of postnasal drainage as a source for cough in patients with rhinosinusitis.[12,13,22,23] The lack of significance in the asthmatic patients suggests that postnasal drainage may not be a significant causative factor for cough in this subgroup. Therefore, treatment for asthma may also impact cough symptoms in this group as an additional benefit beyond complete management for CRS.

Cough has been included as a component of patient reported outcome measures for rhinosinusitis since 1995 as part of the 31-item Rhinosinusitis Outcome Measure (RSOM-31),[24] and the later derived SNOT-20[15] and SNOT-22.[14] Factor analysis of the SNOT-22 has led to the development of subdomains, with inconsistent assignment of cough into "nasal" or "extranasal" domains.[16-18] This may, in part, be reflective of the multifactorial nature of cough and possible etiologies aside from CRS that do not consistently have other symptoms in the nasal subdomain. SNOT-22 parameters have been investigated as predictors of improvement after ESS, and cough was found to have a negative impact on the extent of improvement.[25] The Asthma Control Test (ACT) is a widely used instrument for evaluating asthma control and is correlated with SNOT-22 scores.[26] In patients with CRS and asthma, the cough item of the SNOT-22 is inversely correlated with asthma control measured by ACT.[26] These are also suggestive of multifactorial etiology for cough in CRS patients, and specifically asthma as a possible contributing factor.

The most notable limitation of the current study is that the SNOT-22 cough score item is not independently validated for reporting cough severity or HRQOL effects. Therefore, conclusions regarding cough severity as a predictor for concurrent asthma in CRS patients are limited, and would be best addressed using a validated cough HRQOL instrument. The SNOT-22, however, can be routinely used in the evaluation of CRS patients for assessing multiple related quality of life effects when numerous disease specific instruments are not practical. A prospective study using both the SNOT-22 and a cough specific instrument might help to understand the significance of the SNOT-22 cough item response separate from CRS quality of life effects. An additional limitation is that other factors associated with complaint of cough such as GERD or LPR was not routinely captured in the enrolled patients. Evidence for causation of cough from GERD is incomplete, and there have not been recommendations for routine evaluation and treatment of GERD in CRS patients.[19,27] Therefore, unlike asthma, evaluation for GERD has not been incorporated into our rhinology practice in a standard fashion. Despite the associations reported, causality of asthma for cough in CRS patients cannot be ascertained and should not be implied due to the aforementioned limitations. The lack of correlations between PFT parameters and cough item response also argue against sole causality. Future study could incorporate the three most often cited causes for cough (postnasal drainage, asthma, and GERD), using disease specific instruments and/or objective measures, in a multivariable model in an effort to elucidate a dominant feature. Finally, the retrospective database used does not allow for accurate identification of patients with an acute CRS or asthma exacerbation, and whether this is a confounding factor for cough in CRS patients.

5 | CONCLUSION

In CRS patients, complaint of cough, as reported on the SNOT-22 questionnaire, was associated with diagnosis of asthma. This association was significant in CRSsNP patients, but not CRSwNP patients. Sensitivity in all CRS patients was 73.9% and 83.3% in the CRSsNP subgroup. Specificity of cough for asthma diagnosis was low, and this suggests the potential multifactorial etiology for cough in CRS. Nevertheless, given that asthma was diagnosed in over 38% of CRS patients and has significant prognostic and therapeutic implications, the complaint of cough in CRS patients warrants mindful investigation for asthma. A prospective study designed to address the potential multifactorial etiology for cough in CRS patients would better establish comorbid asthma as a contributor, and possibly define a diagnostic pathway.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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