ORIGINAL ARTICLE

The Sino-Nasal Outcome Test–22 as a tool to identify chronic rhinosinusitis in adults with cystic fibrosis

Al-Rahim R. Habib, MSc[1,2], Bradley S. Quon, MD, MSc[3], Jane A. Buxton, MBBS, MHSc[1],
Saad Alsaleh, MBBS[2], Joel Singer, PhD[1], Jamil Manji, MSc[2], Pearce G. Wicox, MD[3] and Amin R. Javer, MD[2]

Background: Chronic rhinosinusitis (CRS) is becoming increasingly prevalent in adults with cystic fibrosis (CF), as the median age of survival rises for these individuals. Delayed identification of CRS may contribute to worsening health-related quality of life and increased treatment burden. Our objective was to investigate the utility of the 22-item Sino-Nasal Outcome Test (SNOT-22) as a tool to identify CRS in adults with CF.

Methods: In this cross-sectional study, participants were sampled from an adult-specific CF clinic in Vancouver, Canada, between September 2013 and April 2014. CRS was determined by use of standardized diagnostic guidelines. Participants completed the SNOT-22 and medical charts were reviewed for additional predictor variables. Logistic regression was used to compare the SNOT-22 as a univariable predictor variable to a multivariable prediction model, in order to best differentiate CRS and non-CRS participants.

Results: Ninety-three of 101 adults provided written informed consent. The prevalence of CRS was 56.3% (95% confidence interval [CI], 45.9% to 66.3%). Individuals with

CRS reported significantly higher SNOT-22 scores than non-CRS participants (mean difference: 13.9; 95% CI, 6.1 to 21.7). The optimal SNOT-22 score to differentiate CRS was 21 out of 110 (sensitivity: 76%, specificity: 61%, positive predictive value: 71%, likelihood ratio: 1.9).

Conclusion: Compared to the current diagnostic gold standard, SNOT-22 scores greater than 21 sufficiently identified adults with CF presenting with concomitant CRS. The SNOT-22 is a simple instrument that can easily be implemented in adult CF clinics to assist care providers identify individuals requiring more detailed assessment or referral to a sinus clinic. © 2015 ARS-AAOA, LLC.

Key Words:
cross-sectional studies; chronic rhinosinusitis; predictive model; cystic fibrosis; clinical epidemiology

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In the past 4 decades, individuals with cystic fibrosis (CF) have experienced an increase in life expectancy.[1] As adults with CF live longer, extra-pulmonary chronic diseases such as cystic fibrosis-related diabetes, osteoporosis,

depression, and chronic rhinosinusitis (CRS) have increased in prevalence.[2,3] In the non-CF population, epidemiological studies have estimated the prevalence of CRS to range from 5% to 16%.[4–6] It has been estimated that the prevalence of CRS is nearly 4 times higher in the CF population.[7]

Currently, the diagnostic gold standard for CRS involves a combination of subjective and objective components.[8–10] Subjective assessment consists of interviewing patients to evaluate the severity of 5 major sinus symptoms (ie, nasal congestion, facial pain or pressure, nasal obstruction, anterior or posterior nasal discharge, and loss of smell or taste) present for at least 12 weeks. Sinus-specific questionnaires such as the 22-item Sino-Nasal Outcome Test (SNOT-22), Rhinosinusitis Disability Index (RSDI), and Chronic Sinusitis Survey (CSS) are commonly used to measure symptomatology and health-related quality of life.[11–13] Objective findings are evaluated using nasal endoscopy to identify nasal polyps, mucopurulent discharge, and obstruction of the

middle meatus. In conjunction, radiographic imaging of the sinuses can be utilized to evaluate mucosal changes characteristic of CRS. However as a standalone, the subjective and objective components have previously been shown to poorly predict CRS status.[14]

In the CF population, the diagnosis of CRS can be challenging because these individuals underreport or downplay symptoms given the competing medical concerns. Similarly, CF care providers can sometimes overlook CRS as they must manage several comorbidities and balance increasingly complex treatment regimens. Given these circumstances, a predictive model to identify CRS may help improve clinical decision-making by CF care providers. The purpose of this cross-sectional study was to construct a predictive model to identify concomitant CRS in adults with CF. This model might be used by CF care providers to identify individuals who require referral to an otolaryngologist to facilitate earlier treatment, which may contribute to an improvement in health-related quality of life. Some of these findings have been previously reported in the form of an abstract.[15]

Subjects and methods

Study design and recruitment

Adult participants were sampled from the St. Paul's Hospital CF Clinic located within an academic teaching hospital in Vancouver, Canada. Eligible individuals attended the clinic for routine assessment between September 2013 and April 2014 and had a confirmed diagnosis of CF based on standardized criterion.[16] Individuals with history of bilateral lung transplant were excluded. Ethics approval was obtained from the University of British Columbia Clinical Research Ethics Board and all participants included in the study provided written informed consent (approval number: H13-01848).

Conduct of study

Eligible individuals were contacted by mail and phone to participate in this cross-sectional study. Research staff approached individuals interested in participating during their routine CF clinic assessment. Individuals providing written informed consent were directed to the St. Paul's Hospital Sinus Centre to receive a standardized nasal assessment from a senior otolaryngologist (A.R.J). This included an interview about sinus-related symptoms, history of medical or surgical treatment, and completion of the SNOT-22. The SNOT-22 is a previously validated instrument that can differentiate individuals with or without CRS and is used to quantify improvement after surgical or medical interventions.[11,12] Higher scores on the SNOT-22 score indicate greater disease severity and worse health-related quality of life. The SNOT-22 can be categorized into discrete groups, as has been described elsewhere.[12]

Reference standard for the diagnosis of CRS

Participants were diagnosed with CRS based on Canadian Clinical Practice Guidelines.[8] This included an assessment of the 5 major sinus symptoms (ie, nasal congestion, facial pain or pressure, nasal obstruction, anterior or posterior nasal discharge, loss of smell or taste) and objective evaluation for clinical signs of CRS. Individuals considered symptomatic for CRS reported the presence of at least 2 major sinus symptoms (mild, moderate, or severe). Individuals asymptomatic for CRS reported less than 2 major sinus symptoms. Objective findings were evaluated using a 3.0-mm nasal endoscope (Karl Storz GmbH & Co. KG, Tuttlingen, Germany) to identify nasal polyps, discolored mucus, pus, or inflammation within the middle meatus. For individuals refusing nasal endoscopy, clinically requested sinus computed tomography (CT) scans (ie, up to 1 year prior to the conduct of the research study) were reviewed for diagnostic purposes to support the objective component of CRS diagnosis. Participants were excluded if CRS status could not be determined (ie, nasal endoscopy was refused and sinus CT scans were unavailable).

Predictor variables

Several predictor variables were identified a priori based on consultation with clinical experts and included SNOT-22 scores, age (years), gender (male/female), current employment status (yes/no), body mass index (BMI, kg/m^2), age of CF diagnosis (years), class I to III genotype mutations (yes/no),[7] lung function (forced expiratory volume in 1 second [FEV1]% predicted), and chronic *Pseudomonas aeruginosa* infection—defined as 3 positive sputum cultures within 6 months prior to enrollment (yes/no).[17] Additional categorical binary variables recorded were pancreatic insufficiency and active use of antidepressants as an indication for clinically significant depression.

Statistical analysis

Sociodemographic and clinical characteristics of individuals with vs without CRS were evaluated using bivariable methods. Parametric tests (ie, Student t test, chi-square test) were used for continuous variables following a normal distribution and categorical variables with expected cell counts greater than 5. Nonparametric tests (ie, Wilcoxon rank sum, Fisher's exact test) were used for variables that did not meet the parametric test requirements. Mean differences and odds ratios (ORs) were reported with corresponding 95% confidence intervals (95% CIs). All tests were 2-sided and p values <0.05 were considered statistically significant.

Multivariable logistic regression was used to develop a model for the prediction of CRS status using methodology previously described.[18–21] The linearity assumption for logistic regression was assessed by plotting continuous variables against the presence or absence of CRS. Collinearity between predictor variables was assessed using Pearson's correlation coefficient statistic for continuous variables and the chi-square test for categorical variables. The Akaike
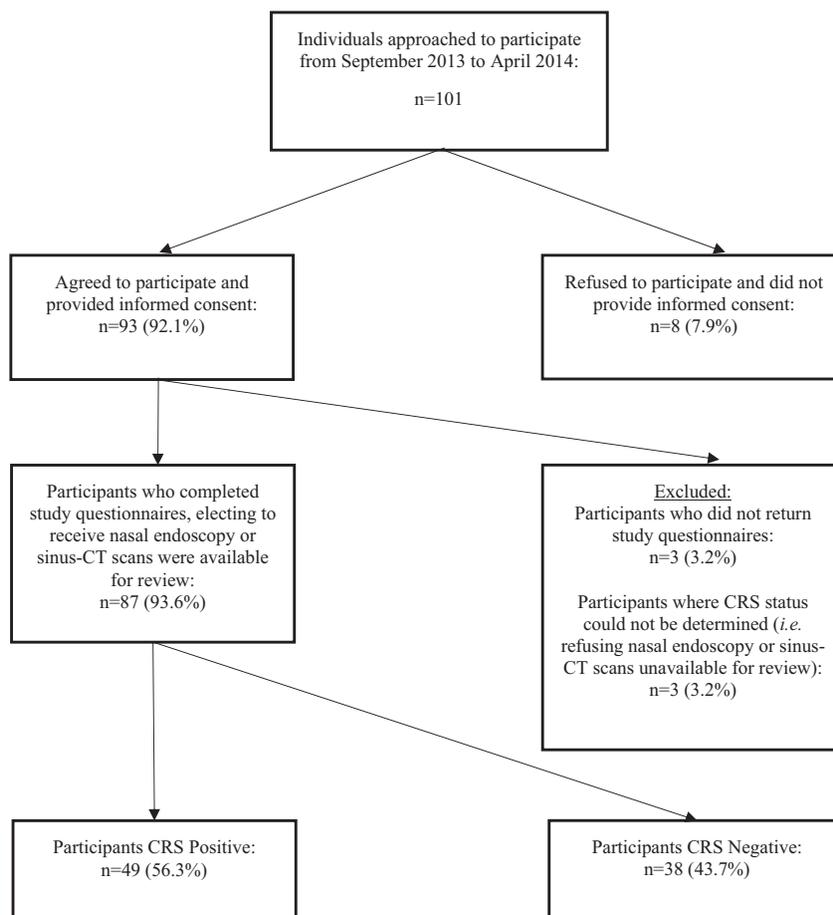
FIGURE 1. Flow diagram describing number and frequency of individuals approached, participating, refusing, completing study questionnaires, CRS-positive, and CRS-negative. CRS = chronic rhinosinusitis; CT = computed tomography.

Information Criterion (AIC) and concordance index (c-index) were used to distinguish models.[21]

To evaluate the ability of the predictive model to distinguish between CRS-positive vs CRS-negative individuals, a receiver operating characteristic (ROC) curve was constructed by plotting the sensitivity (true positive rate) against the false-positive rate ($1 -$ specificity). The area under the ROC curve (AUC) statistic and corresponding confidence intervals were reported to compare ROC curves. The best cutoff score was reported that maximized sensitivity while minimizing the false-positive rate. Statistical analysis was completed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Results

A total of 93 individuals participated in this cross-sectionals study (Fig. 1). Of those that participated, 6 were excluded because they did not return study questionnaires (n = 3) or CRS status could not be determined (n = 3, Fig. 1). The study sample was representative of the total clinic population when compared to previously collected, clinic-specific CF Registry data in terms of age (sample: 35.3 years vs clinic population: 36.1 years), gender (sample: 66.7% male

vs clinic population: 57.5% male), BMI (sample: 23.4 vs clinic population: 22.6 kg/m^2), FEV$_1$% predicted (sample: 72.3% vs clinic population: 73.1%) and mean age of CF diagnosis (sample: 10.4 years vs clinic population: 9.0 years).

The most common sinus symptoms reported among all participants were nasal congestion (70.1%; 95% CI, 59.8% to 78.7%), anterior or posterior nasal discharge (64.4%; 95% CI, 53.9% to 73.6%), and loss of smell or taste (55.2%; 95% CI, 44.7% to 65.2%). The prevalence of CRS was 56.3% (95% CI, 45.9% to 66.3%) and nasal polyposis was 21.0% (95% CI, 12.5% to 33.3%). Among CRS-positive participants (n = 49), all reported ≥2 sinus symptoms and showed objective evidence of CRS from nasal endoscopy (n = 44, 95.6%) or sinus CT scans if nasal endoscopy was refused (n = 5, 100%). Among CRS-negative participants (n = 38), 14 individuals reported ≥2 sinus symptoms without objective evidence of CRS, 12 individuals were asymptomatic despite endoscopic (n = 7), radiographic (n = 3), or evidence of previous sinus surgery (n = 2), and 12 individuals were asymptomatic with no objective evidence identified.

Socioeconomic and clinical covariates did not significantly differ between CRS and non-CRS individuals (Table 1). Individuals with CRS reported significantly worse total

TABLE 1. Comparison of sociodemographic and clinical factors between participants with vs without CRS

Sociodemographic and clinical factors	CRS-positive (n = 49)	CRS-negative (n = 38)	p
Age (years), mean ± SD	34.8 ± 11.7	36.1 ± 14.7	0.65
Males, n (%)	33 (67.4)	25 (65.8)	0.88
Currently employed/attending school, n (%)	30 (61.2)	26 (68.4)	0.49
Body-mass index (kg/m^2), mean ± SD	23.8 ± 3.6	22.9 ± 3.5	0.23
FEV$_1$% predicted, mean ± SD	72.4 ± 25.0	72.3 ± 28.8	0.99
Class I to III CFTR mutations, n (%)	35 (74.5)	24 (68.6)	0.56
Age of diagnosis (years), median (interquartile range)	3.5 (0.8 - 12.0)	4.3 (0.5 - 23.8)	0.90[a]
Current use of antidepressants, n (%)	14 (28.6)	5 (13.2)	0.08
Chronic *P. aeruginosa* infection, n (%)	23 (46.9)	13 (34.2)	0.23

[a]Nonparametric Wilcoxon rank sum test.
CFTR = cystic fibrosis transmembrane receptor; CRS = chronic rhinosinusitis; FEV$_1$ = forced expiratory volume in one second; SD = standard deviation.

TABLE 2. Comparison of SNOT-22 scores between participants with vs without CRS[*]

Sociodemographic and clinical factors	CRS-positive (n = 49)	CRS-negative (n = 38)	P
Total SNOT-22 score (0–110)	35.9 (20.8)	21.9 (15.8)	**0.0006**
Subgroup scores			
Rhinologic-specific (0–35)[a]	12.5 (7.4)	6.9 (5.8)	**0.0001**
Ear-specific (0–20)[b]	3.4 (3.3)	1.9 (3.1)	**0.03**
Sleep-specific (0–15)[c]	5.56 (4.6)	3.4 (3.8)	**0.02**
Psychology-specific (0–30)[d]	11.2 (8.5)	7.3 (7.2)	**0.02**

[*]Values are mean ± SD. Bold values are significant.
[a]Items include: "need to blow nose," "nasal obstruction," "sneezing," "runny nose," "postnasal discharge," "thick nasal discharge," "decreased smell or taste."
[b]Items include: "ear fullness," "dizziness," "ear pain," "facial pain or pressure."
[c]Items include: "difficulty falling asleep," "waking up at night," "lack of a good night's sleep."
[d]Items include: "fatigue," "reduced productivity," "reduced concentration," "frustrated/restless/irritable," "sad," "embarrassed."
CRS = chronic rhinosinusitis; SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcome Test.

SNOT-22 scores than non-CRS counterparts (mean difference: 13.9; 95% CI, 6.1 to 21.7; Table 2). Stratification by SNOT-22 categories showed that CRS-positive participants reported significantly worse rhinologic, sleep, and psychology-related scores than individuals without CRS (Table 2).

Total SNOT-22 score yielded the largest AUC value to differentiate participants with or without CRS (0.70; 95% CI, 0.58 to 0.79; Fig. 2). As indicated by the ROC curve, the optimal cutoff score was 21 out of 110, which resulted in a sensitivity of 76%, specificity of 61%, positive predictive value of 71%, and likelihood ratio of 1.9. SNOT-22 scores did not significantly differ between participants with vs without nasal polyposis (mean difference: 5.2; 95% CI, −10.7 to 21.1).

The multivariable model did not yield a significantly greater AUC value than the univariable SNOT-22 model (multivariable AUC: 0.71; 95% CI, 0.56 to 0.81; univariable AUC: 0.70; 95% CI, 0.58 to 0.79; p = 0.64; Table 3, Fig. 3). This result favors the null hypothesis that the univariable SNOT-22 model does not significantly differ from the multivariable model to differentiate CRS status (Table 3, Fig. 3).

Discussion

As the CF population has shifted in age demographic, CF care providers are frequently encountering patients who present with multiple chronic diseases and an increased treatment burden.[2,3] CRS is a chronic disease that has previously been shown to occur more frequently in adults with CF[6,7] and identification is important for managing health-related quality of life. Previous findings suggest the negative association between CRS and the health-related quality of life observed in the non-CF population[22–24] also exists in adults with CF.[25] Diagnosis of CRS is challenging and often overlooked; therefore, CF care providers may find utility in the SNOT-22 to identify potential patients with concomitant CRS and guide subsequent referral to an otolaryngologist.

The SNOT-22 has been proposed as a predictive tool to identify nasal polyposis in children with CF.[26]

TABLE 3. Comparison of multivariable and univariable logistic regression models to predict CRS in adults with CF

Model characteristics	Multivariable logistic regression model			Univariable logistic regression model		
Akaike Information Criterion	113.25			116.79		
Concordance Index	0.714			0.703		
Predicator variables	β	SE	p^a	β	SE	p^a
Intercept	−0.49	0.36	0.18	−0.19	0.23	0.41
Total SNOT-22 score (1 = SNOT-22 ≥21, 0 = SNOT-22 <21)	0.59	0.25	**0.02**	0.57	0.23	**0.01**
Current use of antidepressants (1 = yes, 0 = no)	0.40	0.33	0.23	–	–	–
Chronic *P. aeruginosa* infection (1 = yes, 0 = no)	0.22	0.26	0.40	–	–	–
Gender (1 = male, 0 = female)	0.03	0.26	0.91	–	–	–
Class I to III mutations (1 = yes, 0 = no)	0.10	0.28	0.73	–	–	–

[a]Bold values are significant.
β = regression coefficient; CF = cystic fibrosis; CRS = chronic rhinosinusitis; SE= standard error; SNOT-22 = 22-item Sino-Nasal Outcome Test.
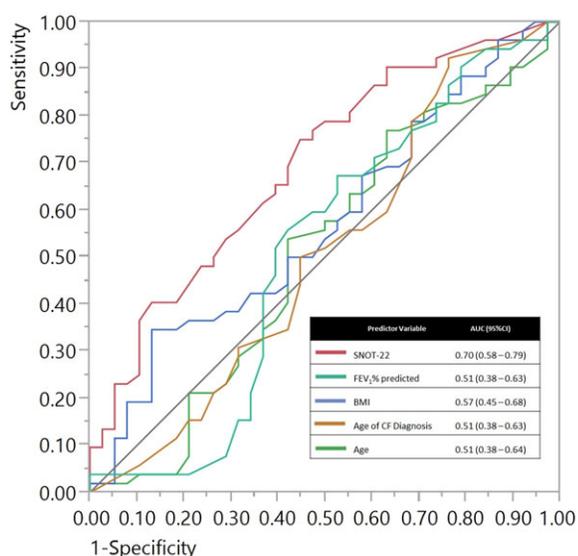

FIGURE 2. Receiver operating characteristics curves of SNOT-22, FEV$_1$% predicted, BMI, age of CF diagnosis, and age to identify best cutoff score to differentiate participants with vs without CRS. AUC = area under the receiver operating characteristic curve; BMI = body mass index; CF = cystic fibrosis; CI = confidence interval; CRS = chronic rhinosinusitis; FEV$_1$ = forced expiratory volume in 1 second; SNOT-22 = 22-item Sino-Nasal Outcome Test.
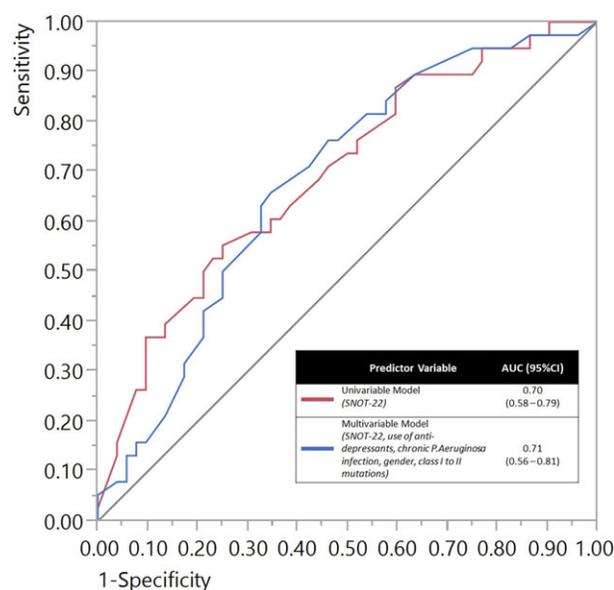

FIGURE 3. Receiver operating characteristics curves for univariable vs multivariable logistic regression models to differentiate participants with vs without CRS. AUC = area under the receiver operating characteristic curve; CI = confidence interval; CRS = chronic rhinosinusitis; SNOT-22 = 22-item Sino-Nasal Outcome Test..

Thamboo et al.[26] found that SNOT-22 scores greater than 11 were significantly associated with endoscopic visualization of concurrent nasal polyposis and, subsequently, recommended referral to an otolaryngologist if these scores are achieved. However these findings may not be generalizable to adults with CF, as SNOT-22 scores between adults enrolled in this study did not significantly differ between those with vs without nasal polyposis. Participants enrolled received standardized assessment to determine CRS status that consisted of endoscopic and radiographic investigations and sinus-related symptomology. These methodological considerations were utilized to establish a SNOT-22

cutoff score suitable for implementation in adult CF centers, given the increasing prevalence of CRS with older age. The best cutoff score to identify CRS is 21 out of 110 points. This cutoff score yields a sensitivity of 76%, specificity of 61% and positive predictive value of 71%. The performance of predictive tools depends predominantly on the choice of cutoff used to define a positive test. Higher cutoffs establish thresholds that fewer patients can achieve, resulting in decreased sensitivity and increased specificity. Lower cutoffs can be achieved more frequently, which contributes to increased sensitivity yet decreased specificity. However, the optimal cutoff selected for the CRS predictive model proposed in this study was chosen to maximize the

positive likelihood ratio and sensitivity, while minimizing the false-positive rate. Individuals achieving or exceeding a cutoff score of 21 are 1.9 times more likely to be positively identified with CRS by an otolaryngologist. This can be alternatively interpreted in a clinical setting using Bayes theorem.[27] Utilizing the pretest probability of CRS found in this study (56%), the posttest probability that an individual is CRS positive is 71% if scoring greater than 21 on the SNOT-22.

Currently, CF-specific diagnostic criteria for CRS are not available. Therefore, this study is limited by the use of non-CF–specific CRS guidelines for the diagnostic reference standard. It is plausible that sinus symptoms may be reported differently between CF and non-CF individuals and this may impact the number of individuals who fulfill the symptom component for CRS diagnosis. This is evident in non-CRS individuals, as 10 of 38 participants were asymptomatic despite visualization of endoscopic or radiographic evidence of CRS. Given this, the prevalence of CRS as per the non-CF specific standardized diagnostic criteria used for the reference standard may underestimate the true prevalence of CRS in adults with CF. A previously conducted cross-sectional study using the similar diagnostic criteria reported a comparable prevalence estimate (63%), as was found in this study (56%).[7] In addition, the SNOT-22 has been previously validated in CRS but alternative questionnaires have been used in studies of adults with CF.[28] Khalid et al.[28] used the RSDI and CSS to quantify health-related quality of life pre–sinus surgery and post–sinus surgery. However, the SNOT-22 is currently the most widely used CRS-specific questionnaire[13] and has been previously been shown to significantly differentiate between individuals with CRS and healthy controls.[11] The SNOT-22 includes 2 additional questions related to "nasal obstruction" and "reduced sense of smell or taste" than its earlier version, the SNOT-20. Browne et al.[12] propose that the SNOT-22/20 is clinically meaningful because it can be considered as a unidimensional score or stratified into discrete categories pertinent to rhinologic-specific, ear-specific, sleep-specific, and psychologic-specific items. Investigating category-specific scores may be useful to CF care providers by illuminating factors other than major sinus symptoms that patients may experience. For example, in this study participants with CRS reported significantly worse sleep and psychological function than non-CRS counterparts. This suggests that CRS impacts several factors of daily life such as sleep quality, fatigue, concentration, and productivity. Similarly, previous epidemiological studies have reported a cross-sectional association between CRS and depression.[24] This may also be apparent in the CF population, because individuals with CRS were over twice as likely to use antidepressants based on findings in this study.

As a single predicator, the SNOT-22 had comparable ability to distinguish CRS status compared to a multivariable logistic regression model that included use of antidepressants, chronic *P. aeruginosa* infection, class I to III cystic fibrosis transmembrane conductance regulator (CFTR) mutations, and gender. These factors were considered because they differed between CRS and non-CRS participants, despite nonsignificant findings. However, comparing AUC values from ROC curves plotted for the univariable and multivariable logistic regression models suggested that SNOT-22 could be as meaningful as a comprehensive regression model. This is advantageous to CF care providers because the SNOT-22 is an easy-to-use instrument that can be implemented into routine clinical practice and calculated without auxiliary software. Patients exceeding the cutoff score of 21 can be evaluated in greater detail for CRS by the attending healthcare team or subsequently referred to an otolaryngologist. Given the increasing prevalence of CRS with older age[1,2] and that CRS adversely impacts on quality of life,[22,23] it is imperative to support CF clinicians to identify patients who may benefit from more aggressive medical therapy or an otolaryngologist referral. CF clinical care is complex and emphasis is appropriately placed on optimizing pulmonary status, but comorbidities such as CRS can be overlooked. The SNOT-22 can be used as a predictive tool to support CF clinicians with a standardized method of quantifying their suspicion of CRS and to reduce variability in treatment and referral patterns. Future studies are required to validate these findings and establish CF-specific CRS diagnostic criteria.

Conclusion

This cross-sectional study investigated the utility of the SNOT-22 to identify concomitant CRS in adults with CF. A total SNOT-22 score of 21 out of 110 was found to optimally differentiate CRS positive and negative individuals. As a single predictor variable, the SNOT-22 yielded similar AUC values as a multivariable logistic regression equation that included several sociodemographic and clinical factors. CF care providers may consider incorporating the SNOT-22 in daily practice to identify potential patients that warrant detailed sinonasal examination or referral to an otolaryngologist. Future studies are required to validate the proposed cutoff score and establish CF-specific guidelines to diagnose CRS.

Acknowledgments

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