Patient-reported chronic rhinosinusitis disease control is a valid measure of disease burden*

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Abstract

Background: Disease control is an important treatment goal for chronic uncurable conditions such as chronic rhinosinusitis (CRS). The objective of this study was to determine whether patient-reported CRS disease control is a valid reflection of disease burden.

Methods: Prospective longitudinal study of 300 CRS patients (35% CRS with nasal polyps, 65% CRS without nasal polyps). At enrollment and at a subsequent follow-up timepoint, all participants were asked to rate their CRS disease control as "not at all," "a little," "somewhat," "very," or "completely", as well as to complete a 22-item Sinonasal Outcome Test (SNOT-22) and the 5-dimension EuroQol general health questionnaire from which the visual analogue scale (EQ-5D VAS) was used.

Results: At enrollment and follow-up timepoints, patient-reported CRS disease control was significantly correlated with SNOT-22 and EQ-5D VAS scores. The change in patient-reported CRS disease control was significantly correlated with change in SNOT-22 and change in EQ-5D VAS scores. There was significant cross-sectional and longitudinal correlation between patient-reported control and all SNOT-22 subdomain scores. A SNOT-22 score of ≤ 25 points or lower, or an EQ-5D VAS score of ≥77 was predictive of having well - (i.e. "very" or "completely") controlled CRS.

Conclusions: Patient-reported CRS disease control is a valid measure of CRS disease burden and general QOL. A patient-reported assessment of CRS disease control could be considered as a component of a more comprehensive measure of CRS disease control.

Key words: chronic rhinosinusitis, disease control, patient-reported outcome measure, SNOT-22, EQ-5D

Introduction

Disease control refers to the extent to which manifestations of a disease are within acceptable limits. For chronic diseases with no possibility of cure, disease control is an important concept and serves as an all-encompassing goal for treatment [1]. As a comprehensive measure of disease status, control implies judgements and values on the choices of specific outcomes or disease manifestations that are incorporated into its calculation. As it implies judgements about which elements of disease are most important and must be managed, any measure of disease control should include the perspectives of the key stakeholders, most conspicuously the affected patients, as well as the providers who care for those patients. The concept of disease control has been well characterized for asthma, a chronic inflammatory condition of the lower airway, and incorporates disease manifestations in the domains of impairment and risk, which are primarily reflective of patients' and healthcare providers' perspectives on which elements of the disease should be minimized through treatment [2,3]. Like for asthma, disease control serves as the goal of treatment for chronic rhinosinusitis (CRS), which is also a chronic uncurable inflammatory condition of the airway [1,4]. The concept of CRS disease control has been proposed over the last decade but nevertheless remains an area of study and development. A comprehensive description of CRS disease control was first proposed based on expert opinion in the 2012 European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) as a reflection of CRS symptoms, need for systemic rescue medications, and objective endoscopic evidence of active mucosal disease [5]. However, the patient perspective on—and the input of patients in—CRS disease control remains poorly understood.

In particular, patients' understanding of the concept of disease control requires greater study. Assessment of control for many diseases incorporates patients' perspectives about their own disease control. Currently, it is unclear to what extent patient-reported CRS disease control could serve as an outcome measure to be incorporated into a global measure of CRS disease control. The objective of this study was to gain greater insight into CRS patients' understanding of CRS disease control by seeking to determine if a measure of patient-reported CRS disease control could serve as a valid measure of disease burden. Moreover, we also believe that the results of this study could inform the decision to incorporate a measure of patient-reported/perceived control into any global measure of CRS disease control.

Materials and methods

Study participants

This study was approved by the University of Cincinnati Institutional Review Board (2019-0397). Adult patients (age 18 years or older) with CRS were recruited prospectively and provided informed consent for inclusion into this study. All participants met consensus, guideline-established criteria for CRS [6]. Exclusion criteria included comorbid diagnoses of vasculitis, cystic fibrosis, sarcoidosis, and immunodeficiency. To remove the confounding effect of recent endoscopic sinus surgery, patients who had a history of endoscopic sinus surgery within the prior 6 months were also excluded.

Study design

This was a longitudinal study. All data were collected at enrollment and the next follow-up timepoint. Demographic information including age and gender was obtained. A smoker was defined as any patient who currently smoked or reported a history of smoking tobacco [7,8]. At enrollment, participants were assessed by the evaluating physician for a history of asthma, diagnosed based on consensus guidelines, as well as a history of aeroallergen hypersensitivity, which was determined through formal allergy testing. Participants were interviewed to identify a history of previous sinus surgery or a history of aspirin sensitivity. The presence of nasal polyps and the history of prior sinus surgery were confirmed on nasal endoscopy.

Outcome measures

At enrollment and follow-up, participants completed all outcome measures. Participants were asked to rate their level of CRS disease control over the last month as "Not at all", "A little", "Somewhat", "Very" or "Completely" [9]. All participants also completed the validated 22-item Sinonasal Outcome Test (SNOT-22) [10], from which the 4 validated (nasal, sleep, ear/facial discomfort, and emotional) subdomains were calculated [11]. All participants also completed the 5-dimension EuroQoL EQ-5D general health-related quality of life (QOL) questionnaire, from which the visual analogue scale (EQ-5D VAS) was used.

Statistical analysis

All analyses were performed using the statistical software package R (www.r-project.org) [12]. This study was powered to detect correlation of small effect size between patient-reported CRS symptom control level and change in SNOT-22 score or change in EQ-5D VAS. Since we did not expect patient-reported control to be an exact reflection of either SNOT-22 or EQ-5D VAS, and we expected variability in SNOT-22 and EQ-5D VAS scores independent of patient-perceived control, we chose to power our study for a small effect size. Correlation was performed with Spearman correlation. For test-retest reliability analysis, 29 of the participants were asked to rate their CRS disease control on 2 occasions that were 1-4 weeks apart, in order to have 80% power at a significance of 0.05 to detect a correlation of large effect size between the two ratings. Predictive ability was calculated using Receiver Operator Characteristic (ROC) curve analysis. The area under the ROC curve (AUC) was calculated with the trapezoid rule and the 95% confidence interval of the AUC was calculated by performing 2000 bootstraps of the data. The 95% confidence interval around threshold values of SNOT-22 score and EQ-5D VAS score maximizing the sum of sensitivity and specificity for prediction of well-controlled CRS was performed by bootstrapping the data 1000 times. Associations between control status and having SNOT-22 score or EQ-5D VAS below/above threshold values was performed with logistic regression from which a log odds ratio [OR] was calculated.

Results

Characteristics of study participants

A total of 300 participants were recruited (105 CRSwNP and 195 CRSsNP). The characteristics of these participants are described in Table 1. There was a mean of 120 days (SD: 94 days) between the enrollment and follow-up time points. Patient-reported CRS disease control changed by a mean of 0.5 (SD: 1.2) levels where each response option in the CRS control question reflected a level. SNOT-22 score changed by a mean of -8.4 points (SD: 17.8 points) while EQ-5D VAS changed by a mean of 3.2 points (SD: 20.9 points).

Patient-reported disease control is cross-sectionally correlated with CRS-specific and general health-related quality of life

We first checked for validity of patient-reported disease control as a reflection of QOL and disease burden by seeking correlation between patient-reported disease control and SNOT-22 score and EQ-5D VAS score (Figure 1). At enrollment, patient-reported disease control was correlated with SNOT-22 ($\rho = -0.42$, $p < 0.001$) and EQ-5D VAS($\rho = 0.31$, $p < 0.001$). At the follow-up time point, we similarly found that patient-reported disease control

Table 1. Characteristics of study participants.

	All participants (N = 300)
Demographics	
Age, mean in years, (SD)	51.1 (16.6)
Gender	
Male	49.3%
Female	50.7%
Smoking	37.0%
Comorbidities	
Aeroallergen hypersensitivity	51.7%
Asthma	27.3%
Aspirin sensitivity	3.3%
CRS characteristics at enrollment	
Nasal polyps	35.0%
Previous endoscopic sinus surgery	38.3%
SNOT-22 score, mean (SD)	41.3 (21.2)
EQ-5D VAS, mean (SD)	66.7 (20.6)
Patient-reported CRS disease control	
Completely	2.3%
Very	8.0%
Somewhat	35.3%
A little	31.7%
Not at all	22.7%

was correlated with SNOT-22 ($\rho = -0.52$, $p < 0.001$) and EQ-5D VAS ($\rho = 0.32$, $p < 0.001$).

Patient-reported disease control is reliable

A subset of 29 participants also reported their level of CRS disease control at two time points 1 to 4 weeks apart. The level of CRS disease control reported at these two times was highly correlated ($\rho = 0.72$, $p < 0.001$), suggesting the reliability of asking patients to report their level of CRS disease control on a 5-item scale.

Change in patient-reported disease control is responsive to changes in CRS-specific and general health-related quality of life

We next checked for responsiveness between changes in the levels of CRS disease control reported by participants and changes in SNOT-22 and changes in EQ-5D VAS (Figure 2). We found that the number of levels of change in patient-reported CRS disease control was correlated with change in SNOT-22 score ($\rho = -0.43$, $p < 0.001$). We also found that the number of levels of change in patient-reported CRS disease control was correlated with change in EQ-5D VAS score ($\rho = 0.24$, $p < 0.001$) Given the responsiveness of patient-reported CRS disease control to

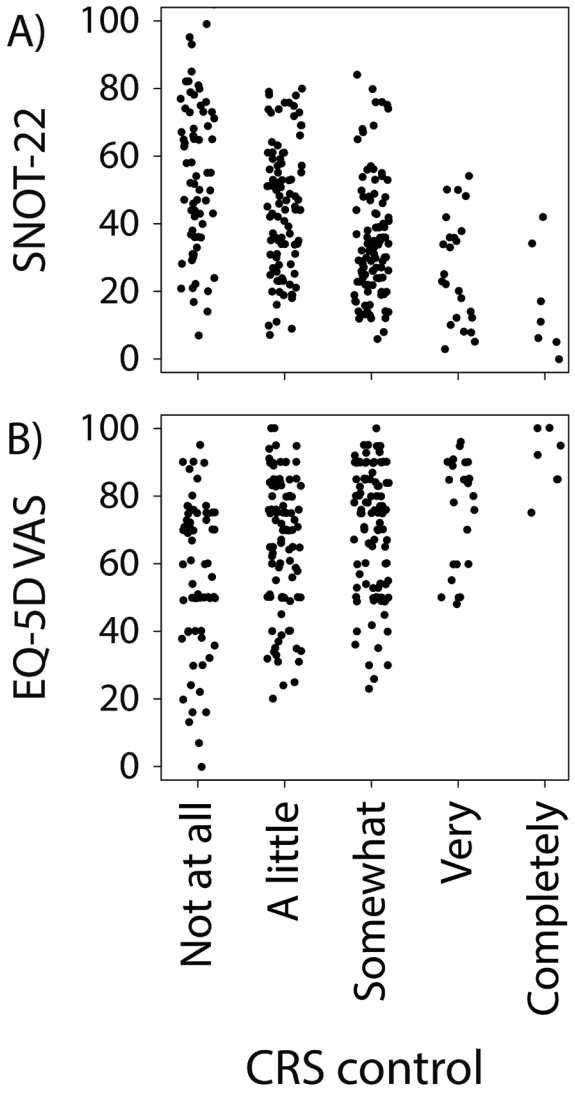

Figure 1. Scatterplot of enrollment patient-reported CRS disease control versus (A) SNOT-22 score, and (B) EQ-5D VAS.

change in the SNOT-22 score, we also checked for its responsiveness to changes in the subdomain scores of the SNOT-22 (Figure 3). We found that the change in the level of patient-reported CRS disease control was correlated with changes in the nasal ($\rho = -0.38$, $p < 0.001$), sleep ($\rho = -0.33$, $p < 0.001$), ear/facial discomfort ($\rho = -0.35$, $p < 0.001$), and emotional ($\rho = -0.22$, $p < 0.001$) subdomain scores.

SNOT-22 score and EQ-5D VAS are predictive of well-controlled CRS

We further examined the relationship between SNOT-22 and EQ-5D VAS scores with patient-reported CRS disease control by investigating the ability of SNOT-22 and EQ-5D scores to predict well-controlled CRS, which we defined as a rating of "very" or "completely" controlled CRS. We found that both

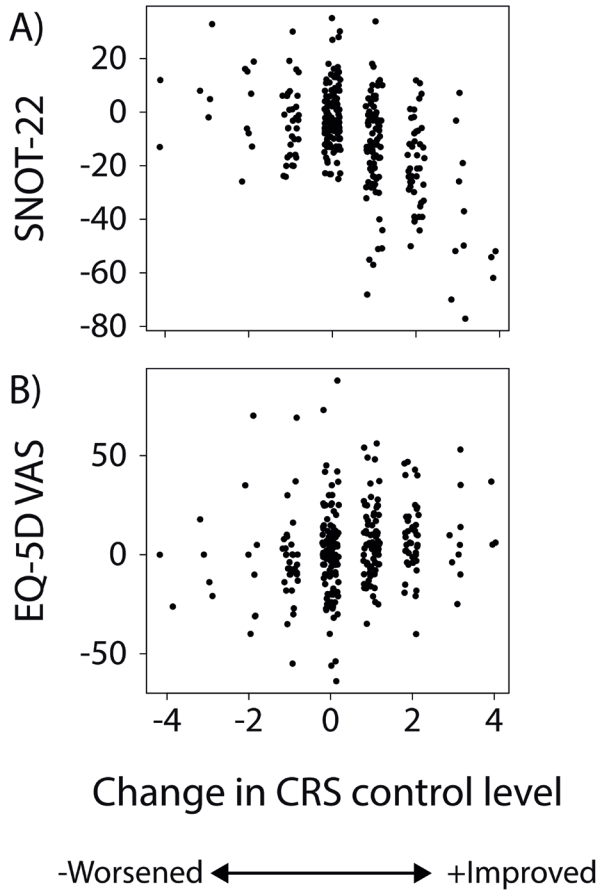

Figure 2. Scatterplot of change in level of patient-reported CRS disease control versus change in (A) SNOT-22 score and (B) EQ-5D VAS.

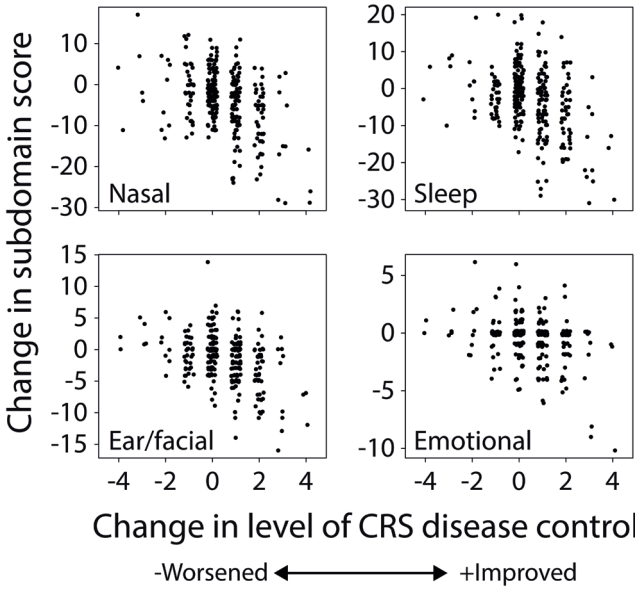

Figure 3. Scatterplot of change in level of patient-reported CRS disease control versus changes in nasal, sleep, ear/facial discomfort, and emotional SNOT-22 subdomain scores.

SNOT-22 score (AUC=0.812, 95%CI: 0.770 – 0.853, p<0.001) and EQ-5D VAS score (AUC=0.707, 95%CI: 0.653 – 0.761, p<0.001) were predictive of well-controlled CRS. A SNOT-22 score of 25 (95%CI: 19 - 40) or lower predicted well-controlled CRS with 72.2% sensitivity and 73.6% specificity. Examined in the other direction, well-controlled CRS was significantly associated with having a SNOT-22 score of 25 or lower (OR: 7.24, 95%CI: 4.5 – 11.5, p<0.001). An EQ-5D score of 77 (95%CI: 76 – 79) or greater predicted well-controlled CRS with 75.0% sensitivity and 66.5% specificity. Well-controlled CRS was also significantly associated with having an EQ-5D VAS of 77 or greater (OR=5.95, 95%CI: 3.70 – 9.55, p<0.001).

Discussion

Disease control may be defined as the extent to which manifestations of a disease are maintained within acceptable limits. As such, it is a construct that is often implemented as the goal of treatment for chronic conditions for which there is no cure. Disease control has been extensively characterized for the care of patients with chronic inflammatory airway conditions such as asthma and allergic rhinitis, and successfully applied to the management of patients with these conditions as a goal of treatment [2,3,13,14]. Determination of disease control criteria for CRS remains an active area for discussion and investigation [1,4]. Previous metrics for evaluation of CRS disease control have been reported. Most prominently, recommendations proposed by the EPOS guidelines assess CRS disease control based on the burden of symptoms, the use of antibiotics and systemic steroids, and endoscopic evidence of active mucosal inflammation [4,5]. Previously described, validated metrics of disease control for asthma and allergic rhinitis have included a patient-reported assessment of overall disease control as a means for direct patient input in relation to the control construct that is being measured [15-18]. Because disease control is likely a complex construct, which may vary in its composition from patient to patient, and CRS has many manifestations including its associated symptomatology [19,20], exacerbations [21-23] which require systemic antibiotics or corticosteroids [24-27], exacerbations of comorbid pulmonary disease [28-32], and social consequences such as missed work or activity avoidance, patient input on assessment of control is paramount [33-36]. A direct assessment of patient-reported CRS disease control that could potentially capture patients' internal synthesis of disease manifestations to form their overall disease experience may therefore serve a valuable role in a global assessment of CRS disease control. The objective of our study was to provide validation for patient-reported CRS disease control as a reflection of CRS disease burden. Because CRS disease control is a multi-factorial concept and we stress that many different disease manifestations may impact a patient's concept of their

disease control (i.e. what manifestations should be kept within acceptable limits), we performed our validation of patient-reported CRS disease control with respect to QOL, which is the major impact of CRS on patients and also what we have previously found to be the major determinant of patient-perceived CRS control [9]. We found that a single question asked of patients to assess their degree of CRS disease control was valid as a reflection of CRS-specific and general health-related QOL, reliable, and responsive to changes in CRS-specific and general health-related QOL. We believe that these results show implicit patient understanding of the concept of the disease control for CRS. Our results also show that a patient-reported measure of CRS disease control could serve as a valid means for direct patient input with respect to the construct of disease control as an outcome measure.

Previous work has shown that patient-reported CRS symptom control was cross-sectionally reflective of CRS-specific QOL and CRS symptom burden [37], and general health-related QOL [38]. More recently, we have used a measure of patient-reported CRS disease control to gain insight into the most dominant determinants of patients' views of their disease control [9]. With nasal symptoms of CRS found to be most associated with patient-reported CRS disease control [9], the specific symptoms of nasal obstruction and nasal drainage have since been reported to be the nasal symptoms most dominantly associated with patient-reported CRS disease control [39]. Beyond the need for a validated explicit measure of patient-reported CRS disease control in global metrics of CRS disease control, a validated measure of patient-reported CRS disease control will also serve as an important tool for the study of determinants of how patients view and assess their CRS disease control.

In this study, we assessed the validity of patient-reported CRS disease control on a 1-month time scale to be consistent with the recall period used to assess CRS symptoms by EPOS CRS disease control guidelines. However, more recent work by our group has also suggested that a 1-month recall period for CRS disease burden may best balance patients' confidence in their recall ability as well as balance patient perspectives on timescales to be used for assessment of their current disease state as well as for clinical decision-making with respect to treatments including endoscopic sinus surgery [40].

We found that a single question that asks patients to report their CRS disease control over the preceding month on a 5-item ordinal response (including options "Not at all", "A little", "Somewhat", "Very" or "Completely") is a valid, reliable and responsive measure of CRS disease burden reflected by CRS-specific and general health-related QOL. However, we again stress that disease control is a concept that likely extends beyond just the impact of CRS on QOL and this likely explains the weak to moderate correlations of patient-reported CRS disease control with the SNOT-22 and EQ-5D VAS. In other words, there is overlap, consistent with our previous finding of CRS symptoms as the dominant determinant of patient-reported CRS disease control [9], but disease control and QOL are not the same things.

We also found that well-controlled CRS (a disease control rating of "very" or "completely") is associated with well-described clinical correlates of the SNOT-22 and EQ-5D VAS. Well-controlled CRS was associated with having a SNOT-22 score of lower than approximately the range of 20 to 40, which has previously been found to be the range in which patients may become candidates for ESS [41-43]. Similarly, we find that well-controlled CRS is associated with having an EQ-5D VAS greater than approximately 80, which is also a threshold previously identified as having good general health-related QOL [44]. These associations between patient-reported CRS control and previously described clinical benchmarks of disease control provide greater confidence in the validity of patients providing input about their own disease.

Our study has implications for the continued development of tools to assess CRS disease control. Various measures of CRS disease control have been developed. The EPOS guidelines recommend assessment of CRS disease control by assessing the burden of nasal blockage, drainage, olfaction, facial pain and poor sleep quality over the preceding month, with the need for rescue medications (antibiotics and systemic corticosteroids) in the preceding 6 months and the objective finding of active mucosal disease on nasal endoscopy [4,5]. A subsequent study of the EPOS control guidelines suggested using only the NOSE system—which assesses the burden of nasal obstruction, the need for rescue medications and endoscopic findings from the EPOS guidelines—to assess CRS disease control [45]. More recently, the Sinus Control Test was developed to assess CRS disease control by querying the burden of nasal obstruction and drainage, CRS-related productivity loss, CRS-related antibiotics or oral corticosteroids usage—all over the preceding 2-week period [46,47]. Although all of these scales do incorporate components—in particular nasal symptoms of CRS—that have been found to be dominantly associated with patient-reported CRS control, none of these scales directly and explicitly assesses how patients perceive their level of CRS disease control—a complementary and potentially more comprehensive picture of how patients' view their disease status. Future development of CRS disease control tools may consider the inclusion of a patient-reported disease control assessment.

Conclusion

The systematic derivation for the definition of CRS control requires continued, focused research on the topic. As CRS is a disease with many manifestations that interact and are synthesized in a patient-specific manner to form the overall disease experience for the patient, the definition of one unified concept of CRS control requires careful study of each possible included element. Moreover, any global definition of CRS disease control requires

input from all stakeholders including healthcare providers, who are not addressed in our study. Nevertheless, our study suggests that an explicit patient-reported measure of disease control may be one option for inclusion into a global metric of CRS disease control.

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Authorship contribution

KMP: concept of study, collection of data, analysis of results, write up of manuscript, critical review of all contents; FAH: collection of data, write up of manuscript, critical review of all contents; KWS: collection of data, write up of manuscript, critical review of all contents; LMB: collection of data, write up of manuscript, critical review of all contents; ARS: concept of study, collection of data, analysis of results, write up of manuscript, critical review of all contents.

Conflict of interest

The authors declare that there are no conflicts of interests regarding the publication of this paper.

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