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ORIGINAL ARTICLE

CRS-PRO and SNOT-22 correlations with type 2 inflammatory mediators in chronic rhinosinusitis

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Abstract: The 22-item Sino-Nasal Outcome Test (SNOT-22) and 12-item Patient Reported Outcomes in Chronic Rhinosinusitis (CRS-PRO) instrument are validated patient-reported outcomes measures in CRS. In this study we assess the correlation of these with type 2 (T2) biomarkers before and after endoscopic sinus surgery (ESS).

Methods: Middle meatal mucus data were collected and the SNOT-22 and CRS-PRO were administered to 123 patients (71 CRS without nasal polyps [CRSsNP], 52 CRS with nasal polyps [CRSwNP]) with CRS before and 6 to 12 months after undergoing ESS. Interleukin (IL)-4, IL-5, IL-13, and eosinophilic cationic protein (ECP) were measured using a multiplexed bead assay and enzyme-linked immunoassay. Pre- and post-ESS SNOT-22 and CRS-PRO were compared with T2 biomarkers.

Results: Before ESS neither PROM correlated with any biomarker. After ESS, CRS-PRO showed a correlation with 2 mediators (IL-5 and IL-13: $p = 0.012$ and 0.003, respectively) compared with none for the SNOT-22. For CRSwNP patients, pre-ESS CRS-PRO and SNOT-22 correlated with IL-4 ($p = 0.04$ for both). However, after ESS, CRS-PRO correlated with 3 biomarkers (IL-5, IL-13, and ECP: $p = 0.02$, 0.024, and 0.04, respectively) and SNOT-22 with 2 biomarkers (IL-5 and IL-13: $p = 0.038$ and 0.02, respectively). There were no significant relationships between any of the T2 biomarkers pre- or post-ESS among patients with CRSsNP. Exploratory analyses of the subdomains showed the SNOT-22

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rhinologic and CRS-PRO rhinopsychologic subdomains correlated better with the T2 biomarkers. On individual item analysis, IL-13 correlated significantly post-ESS with 8 of 12 items on the CRS-PRO vs 6 of 22 items on the SNOT-22.
Conclusion: The CRS-PRO total score showed a significant correlation with T2 biomarkers especially when assessed post-ESS and among CRSwNP patients.

KEYWORDS
CRS-PRO, CRSsNP, CRSwNP, patient-reported outcomes, SNOT-22, type 2 inflammation

1 | INTRODUCTION

Chronic rhinosinusitis (CRS) is prevalent disease that has conventionally been categorized based on 2 phenotypes: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP).[1–3] This phenotypic classification does not accurately portray the true pathophysiology and nature of disease between subtypes. Use of inflammatory biomarkers to categorize CRS patients based on inflammatory subtype has recently led to an increased understanding of the pathophysiology of traditionally phenotypic subtyping.[4–6] Type 2 (T2)-mediated inflammation is now known to be a predominant component of the pathophysiology in 80% to 90% of CRSwNP patients and 30% to 50% of CRSsNP patients in Western countries.[7,8] Although endotypically more heterogeneous, T2 inflammation is still the most common endotype identified in CRSsNP patients.

The T2-inflammatory cascade includes cytokines such as IL-4, IL-5, and IL-13. Each of these individual interleukins has a specific role in the T2-inflammatory cascade from promoting T-helper 2 cell differentiation to increasing eosinophil recruitment.[4] Before the description of these inflammatory cascades, T2 inflammation was frequently recognized histologically by the aggregation of eosinophils within CRS tissue. Eosinophil density has been measured by various semiquantitative means or using concentrations of eosinophil granule proteins such as eosinophilic cationic protein (ECP).[9] While measures of eosinophil density and T2 cytokines are moderately correlated in CRS tissue, it remains unclear whether each of these T2 mediators has similar clinical or symptomatic manifestations. However, multiple clinical trials assessing precision biologics that target individual cytokines, their receptors, or other mediators involved in T2 inflammation have established pathogenicity of this type of inflammation in CRSwNP.[10–13]

CRS morbidity is primarily due to its symptomatic burden, although airway manifestations, such as asthma and bronchiectasis, are increasingly recognized.[14,15] Consequently, patient-reported outcome measurements (PROMs) are important measures of patient's experience, particularly in clinical trials.[16] The 22-item Sino-Nasal Outcome Test (SNOT-22) is among the most widely utilized and validated PROMs to study patients with CRS. However, it is a modification of the longer 31-item Rhinosinusitis Outcomes Measure (RSOM-31) that was developed with little documented input from patients with contemporary definitions of CRS, especially CRSwNP. Furthermore, the modifications to the RSOM-31 to generate the SNOT-22 were driven by physician needs rather than patient-driven input, which contravenes US Food and Drug Administration guidance for PRO instruments acceptable for use as endpoints in clinical trials.[17–20] We recently developed the 12-item Patient Reported Outcomes in Chronic Rhinosinusitis (CRS-PRO), a PROM with extensive documented input from patients diagnosed with CRSwNP and CRSsNP. We validated the instrument and found it to be responsive to both medical and surgical therapy and convergent validity with other measures of CRS, such as radiographic severity as measured by Lund-Mackay score. We found that the shorter CRS-PRO has equal responsiveness and a better correlation with radiographic changes after medical management or endoscopic sinus surgery when compared with the longer SNOT-22. [21-23]

PROMs are developed to represent the patient experience with a specific condition and, frequently, the individual questions fall into groups of different symptoms that reflect a similar concept. The SNOT-22 has been broken down into 5 distinct symptom domains via factor analysis. These include the rhinologic, extranasal, ear/facial, psychologic, and sleep disturbance subdomains.[24] Similarly, a recent factor analysis of the CRS-PRO revealed 3 distinct subdomains: rhinopsychologic, facial discomfort, and cough.[23] These symptom domains are aggregations of individual questions whose responses track with each other

and may reflect sources of variance on a PROM. In another analysis, the rhinologic subdomain of the SNOT-22 was found to be the only domain that correlated with specific T2 inflammatory cytokines. We had not previously evaluated the CRS-PRO instrument, or its subdomains, and their relationship with the T2 biomarkers found in CRS. In the present study, we assessed the correlations of CRS-PRO with T2-inflammatory mediators before and after ESS in patients with CRS and compared the findings with the SNOT-22.

2 | PATIENTS AND METHODS

2.1 | Patient enrollment

In this study we prospectively recruited CRS patients who had undergone ESS at Northwestern Memorial Hospital and had previously consented to collection of middle meatal secretions for our biorepository between 2017 and 2020 (IRB No. STU00016917). Patients were prospectively invited to participate in a research evaluation 6 to 12 months post-ESS. Patients were provided separate written informed consent to access previously collected tissue and clinical information, undergo a research-related examination that included a computed tomography (CT) scan, endoscopy, and administration of PROMs. The CT scans were scored according to total Lund-Mackay (LM) scores.[25] The Northwestern IRB reviewed the study and approved the protocol (IRB STU000202510).

2.2 | PROM administration

PROMs were collected using the CRS-PRO and SNOT-22. These were acquired before ESS and at 6- to 12-month post-ESS follow-up. Scores for each individual question were recorded and total score as well as each subdomain score were recorded for each individual survey.[23,24] For all these measures, an increase in disease severity is indicated by a higher score (SNOT-22: range, 0-110; CRS-PRO: range, 0-48).

2.3 | Mucus acquisition and analysis

Details regarding collection and processing of mucus samples have been described elsewhere.[26] Briefly, at the time of surgery, perioperative antibiotic and steroid medications were held before sample collection. Prepunched ⅜-inch hydroxylated polyvinyl acetate (Medtronic, Minneapolis, MN) sponges were placed in the middle meatus under endoscopic guidance and kept for 10 minutes. This was done immediately before ESS in the operating room and repeated at the clinic post-ESS visit. Mucus samples were eluted from the sponge with centrifugation after adding 100 μL of phosphate-buffered saline with 1% protease inhibitor cocktail (Sigma Co, St. Louis, MO).

The quantification of inflammatory cytokines in middle meatal secretions was assessed using commercially available bead-based multiplex assays (MILLIPLEX MAP Human Luminex, EMD Millipore, Burlington, MA) for interleukin (IL)-4, IL-5, and IL-13. The level of ECP was measured using a commercially available enzyme-linked immunoassay for ECP (MBL, Woburn, MA). The minimal detection limits for IL-4, IL-5, and IL-13 using this kit are 1.83, 0.48, and 0.24 pg/mL, respectively. Values read as below the minimal detection limit were replaced with a value that was half of the lowest detectable threshold for each cytokine. There were no values that were above detectable limits for the cytokines and no values for ECP that were outside detectable limits.

2.4 | Statistical analysis

Statistical analysis was carried out using GraphPad Prism version 9 (GraphPad Software, La Jolla, CA). Descriptive categorical data are presented as frequency count and percent. Descriptive continuous data are presented as median and interquartile range (IQR) when non-normally distributed and as mean and standard deviation (SD) where normally distributed. Correlational analysis was performed using Spearman correlations for nonparametric data sets. The Pearson chi-square test was used to compare differences in categorical data between groups. The r values were interpreted according to strength of correlation, with $r = 0.2$ to 0.4 considered weak, $r = 0.41$ to 0.6 moderate, and $r > 0.6$ strong. The primary group comparisons of interest were the relationships between the CRS-PRO and SNOT-22 total scores and the individual T2 biomarkers. The Benjamini-Hochberg procedure for multiple testing was carried out on the 8 separate correlations with the PROM total scores and each of the T2 biomarkers. Multiple testing correction was done separately for each inflammatory subgroup (total cohort, CRSwNP, CRSsNP) evaluating all correlations within that group before and after ESS. Further exploratory analysis of the subdomain structure of each of the instruments and items was also carried out. The threshold for significance in these analyses was not adjusted for multiple correction. $p < 0.05$ was considered statistically significant for adjusted and exploratory analyses. Although exploratory analyses were not adjusted for multiple corrections, we cited instances of when multiple related items (eg, within a subdomain) showed a significant association.

TABLE 1 Baseline demographics and pre-/post-ESS symptom scores

	CRSsNP (n = 71)	CRSwNP (n = 52)	*p*Value
Age, years	45.9 (15.2)	46.5 (14.2)	0.81
Sex, male, n (%)	33 (47%)	27 (52%)	0.55
Atopic, n (%)	26 (37%)	27 (52%)	0.09
Pre-INCS, n (%)	18 (25%)	18 (35%)	0.27
Smoking, n (%)	16 (23%)	14 (27%)	0.58
Asthma, n (%)	35 (49%)	31 (60%)	0.26
Revision ESS, n (%)	23 (32%)	26 (50%)	0.049[a]
Pre-ESS CRS-PRO score	25.9 (7.3)	25.7 (10.7)	0.92
Pre-ESS SNOT-22 score	48.4 (19.7)	45.0 (20.1)	0.42
Post-ESS CRS-PRO score	11.0 (11.0)	7.0 (13.0)	0.004
Post-ESS SNOT-22 score	21.5 (17.75)	11 (22.5)	0.031
Pre-ESS Lund-Mackay score	9.5 (4.0)	15.3 (4.0)	<0.001

CRS-PRO = 12-item Chronic Rhinosinusitis-Patient Reported Oucome; CRSsNP = CRS without nasal polyps; CRSwNP = CRS with nasal polyps; ESS = endoscopic sinus surgery; INCS = inhaled nasal corticosteroids; SNOT-22 = 22-item Sino-Nasal Outcome Test.

3 | RESULTS

A total of 123 patients undergoing ESS for CRS (CRSsNP: n = 71; CRSwNP: n = 52) were prospectively enrolled. The patient populations of those with CRSsNP and CRSwNP showed no significant difference with regard to age, sex, atopic status, tobacco use, and asthma status. CRSwNP patients were slightly more likely to have undergone revision surgery (50% vs 32%, $p = 0.049$) (Table 1). Before ESS, the CRSwNP patients had more severe LM than the CRSsNP patients (15.3 [SD 4.0] vs 9.4 [SD 4.0], $p < 0.001$). Pre-ESS PROM scores showed no significant difference on either the CRS-PRO and SNOT-22 when comparing CRSwNP vs CRSsNP phenotypes, although only 78% (n = 86) of patients completed these before ESS. After ESS, both the CRS-PRO and SNOT-22 showed a significantly lower total survey score for CRSwNP patients compared with CRSsNP patients (Table 1).

3.1 | Total cohort correlations between T2 mediators and PROM

Pre-ESS Spearman correlations of the SNOT-22 and CRS-PRO and each of the T2 mediators measured from the contemporaneously obtained middle meatal sample for the entire CRS cohort revealed no significant correlations with either the CRS-PRO or SNOT-22. When considering the subdomains of each instrument, the rhinopsychologic subdomain of the CRS-PRO correlated with IL-4, IL-13, and ECP ($r = 0.24, 0.38, 0.38$ and $p = 0.045, 0.001, 0.001$, respectively), as compared with only IL-13 and ECP on the rhinologic subdomain of the SNOT-22 ($r = 0.29, 0.29$ and $p = 0.012, 0.010$, respectively) (Fig. 1A).

In the full patient cohort post-ESS, CRS-PRO total score correlated with contemporaneous IL-5 and IL-13 ($r = 0.28, 0.34$ and adjusted p value $= 0.012, 0.003$, respectively), whereas the SNOT-22 total score correlated with none of the biomarkers. The CRS-PRO rhinopsychologic and SNOT-22 rhinologic subdomains each correlated with IL-4, IL-5, and IL-13 ($r = 0.21, 0.30, 0.36$ and $p = 0.028, 0.002, 0.0001$, respectively; and $r = 0.23, 0.32, 0.35$ and $p = 0.014, 0.0007, 0.0002$, respectively), respectively, in the full patient cohort (Fig. 1B).

3.2 | CRSwNP cohort correlations between T2 mediators and PROM

For CRSwNP patients, the pre-ESS the total score of the CRS-PRO correlated with IL-4 ($r = 0.43$, adjusted $p = 0.04$) and the SNOT-22 total score correlated with IL-4 ($r = 0.39$, adjusted $p = 0.04$). The pre-ESS CRS-PRO rhinopsychologic subdomain correlated more strongly with pre-ESS IL-4, IL-5, and IL-13 ($r = 0.44, 0.48, 0.44$ and $p = 0.01, 0.005, 0.01$, respectively) compared with the rhinologic subdomain of the SNOT-22, which only correlated with IL-4 ($r = 0.39$, $p = 0.049$) (Fig. 2A).

For CRSwNP patients post-ESS, the CRS-PRO correlated with IL-5, IL-13, and ECP, but the SNOT-22 correlated only with IL-5 and IL-13 (CRS-PRO: $r = 0.38, 0.44, 0.335$, adjusted $p = 0.02, 0.024, 0.04$, respectively; SNOT-22: $r = 0.35, 0.41$, adjusted $p = 0.038, 0.02$, respectively). The post-ESS rhinopsychologic subdomain of the CRS-PRO correlated with IL-4, IL-5, and IL-13 ($r = 0.30, 0.38, 0.40$ and $p = 0.048, 0.01, 0.007$, respectively), whereas the rhinologic subdomain of the SNOT-22 correlated with IL-4, IL-5, IL-13, and ECP ($r = 0.32, 0.41,$

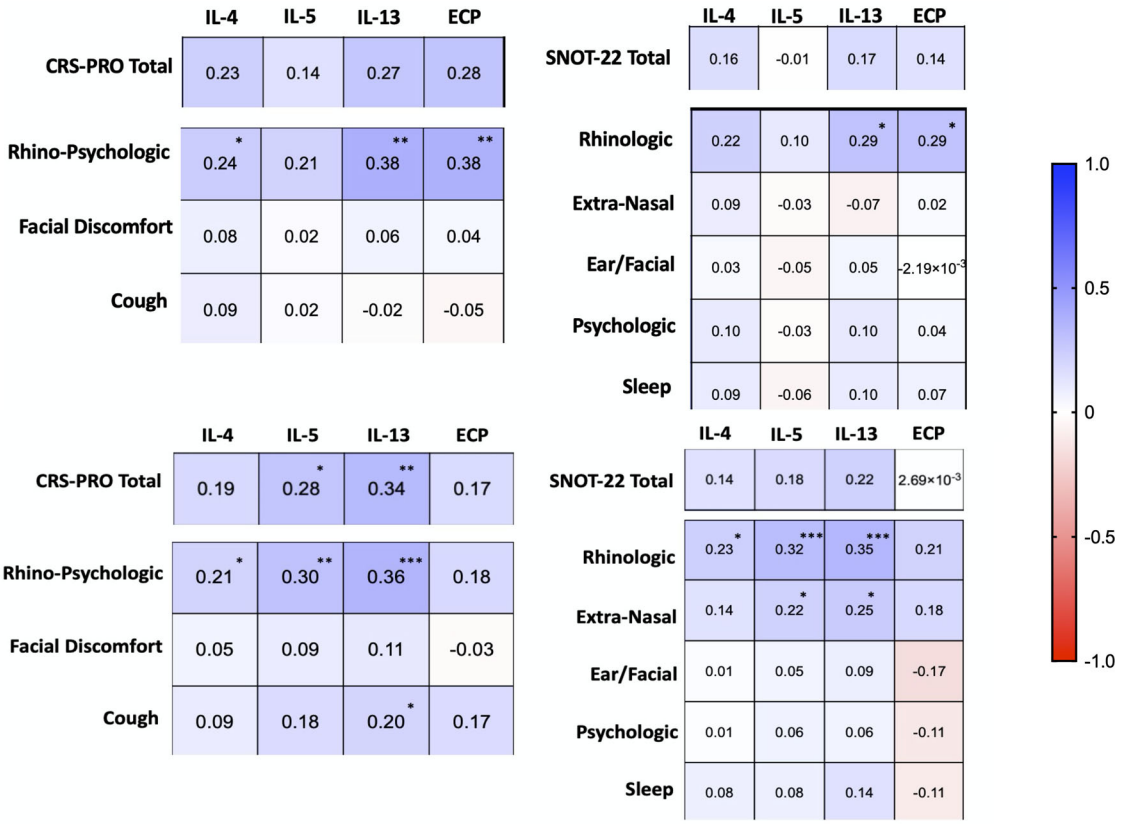

FIGURE 1 Entire CRS cohort correlation between type 2 mediators and the CRS-PRO (A) pre-ESS and (B) post-ESS Spearman correlation coefficients between contemporaneous middle mucus cytokine measures with the PROM total score and their individual subdomains in heatmap format. Blue gradient: positive correlation; red gradient: negative correlation. Spearman correlation *r* values depicted in center of corresponding boxes ($^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.). CRS = chronic rhinosinusitis; CRS-PRO = 12-item Chronic Rhinosinusitis-Patient Reported Oucome, SNOT-22 = 22-item Sino-Nasal Outcome test; ESS = endoscopic sinus surgery; PROM = patient-reported outcome measurement

0.46, 0.35 and $p = 0.03$, 0.005, 0.002, 0.02, respectively) (Fig. 2B).

3.3 | CRSsNP cohort correlations between T2 mediators and PROM

Among CRSsNP patients pre-ESS, neither the total score on the CRS-PRO nor the SNOT-22 correlated with any T2-inflammatory biomarker measured. However, the rhinopsychologic subdomain of the CRS-PRO did correlate with ECP pre-ESS ($r = 0.31$, $p = 0.048$) (Fig. 3A).

In CRSsNP patients, post-ESS the CRS-PRO and SNOT-22 showed no correlation between any biomarkers and PROM. The rhinopsychologic subdomain of the CRS-PRO and rhinologic subdomain of the SNOT-22 in CRSsNP patients post-ESS correlated with IL-5 and IL-13 ($r = 0.27$, 0.33 and $p = 0.03$, 0.007 and $r = 0.32$, 0.26 and $p = 0.01$, 0.04, respectively) (Fig. 3B).

3.4 | Individual question analysis

We then evaluated the individual items from the CRS-PRO and SNOT-22 that contributed to a stronger correlation with the CRS-PRO in the post-ESS setting among the whole cohort of patients. We chose to perform an individual item analysis on the IL-13 specifically because it had the broadest correlation with both subtypes and timepoints. The correlation coefficients for each question with 95% confidence intervals were calculated (Fig. 4). In the overall CRS cohort, IL-13 correlated more often with the CRS-PRO (8 of 12 items) than with the SNOT-22 (6 of 22 items) ($p = 0.026$). The items that correlated were heavily concentrated in the rhinopsychologic subdomains of the CRS-PRO and rhinologic subdomain of the SNOT-22. The 2 items included in the SNOT-22 rhinologic subdomain that did not correlate were sneezing and postnasal drip, which were not developed, or were differently worded, in the CRS-PRO. For example, the postnasal drip question in the rhinologic domain of the SNOT-22 did not correlate,

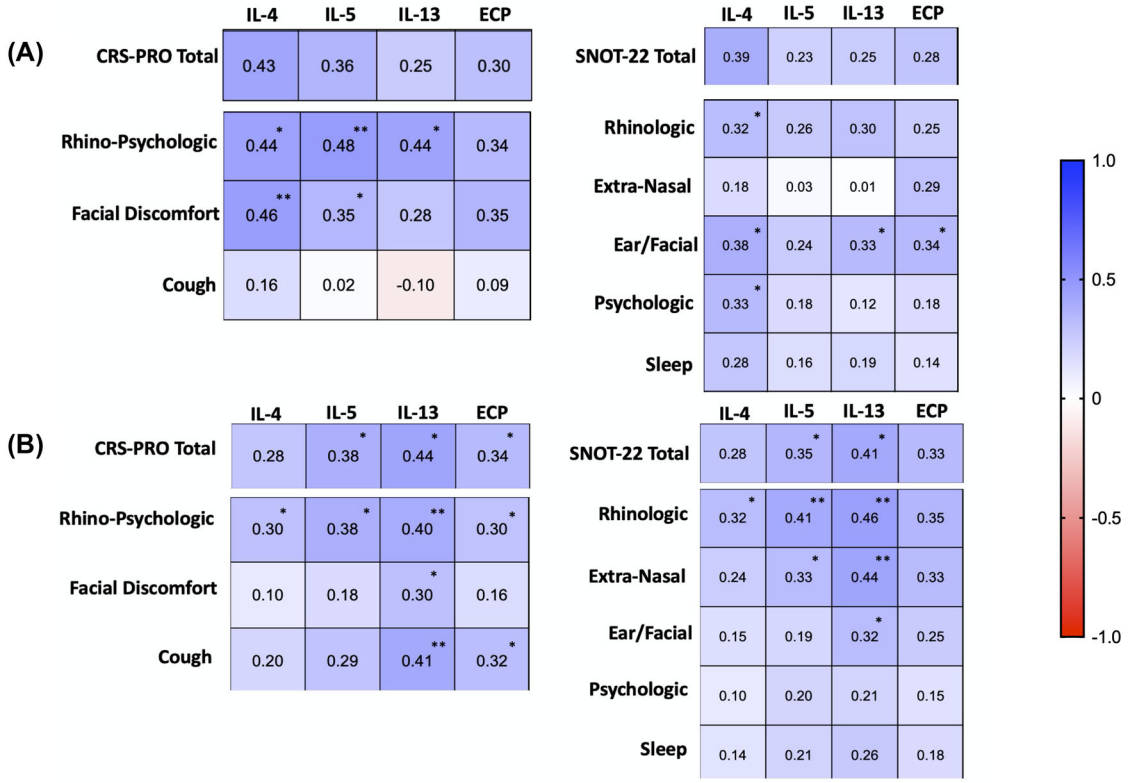

FIGURE 2 CRSwNP cohort correlation between type 2 mediators and the CRS-PRO (A) pre-ESS and (B) post-ESS Spearman correlation coefficients between contemporaneous middle mucus cytokine measures with the PROM total score and their individual subdomains in heatmap format. Blue gradient: positive correlation; red gradient: negative correlation. Spearman correlation *r* values depicted in center of corresponding boxes ($^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$). CRS-PRO = 12-item Chronic Rhinosinusitis-Patient Reported Oucome; CRSwNP = CRS with nasal polyps; ESS = endoscopic sinus surgery; PROM = patient-reported outcome measurement

whereas a similar concept, "I had mucus in my throat," which is in the cough subdomain of the CRS-PRO did show a correlation.

4 | DISCUSSION

The aim of this study was to assess the relationship of PROMs with T2-inflammatory mediators when measured from middle meatal secretions in patients with CRS of both phenotypes, before and after ESS. In addition, we investigated the relationship of T2 inflammation with the newly developed CRS-PRO in comparison to the widely utilized SNOT-22 in both these settings. Neither instrument showed a correlation with any T2 biomarker in patients pre-ESS, except for IL-4, which was significantly correlated with both instruments in CRSwNP patients. In the total cohort of CRS patients post-ESS, disease severity, as measured by the CRS-PRO, showed a significant correlation with 2 critical T2 cytokines, IL-5 and IL-13, compared with no correlation on the SNOT-22. When only responses by patients who previously had CRSwNP were considered, T2-inflammatory mediator concentrations post-ESS were significantly correlated with both the CRS-PRO and SNOT-22, but were consistently stronger with the CRS-PRO (Fig. 2A, B). Both CRS-PRO and SNOT-22 total scores demonstrated no correlation with any T2 measure among pre- or post-ESS CRSsNP patients (Fig. 3B). Of the various T2 biomarkers, IL-13 most frequently correlated with the CRS-PRO and SNOT-22 in the post-ESS setting. Our results indicate that the CRS-PRO correlated better with T2-inflammatory mediators when measured after ESS, especially among CRSwNP patients.

Earlier studies investigating the relationship between PROMs and inflammatory biomarkers have primarily used the SNOT-22 on pre-ESS patients, with cytokines measured in nasal mucus or sinonasal tissue.[27,28] Those results have been mixed. One study evaluated the SNOT-22, in a cohort of both CRS phenotypes pre-ESS, in relation to mucus levels of IL-4, IL-5, and IL-13, and showed that the rhinologic subdomain, but not the total score, correlated with mucus levels of only IL-4—but these results were not adjusted for multiple testing.[27] However, the same authors later stratified a slightly larger group of patients pre-ESS

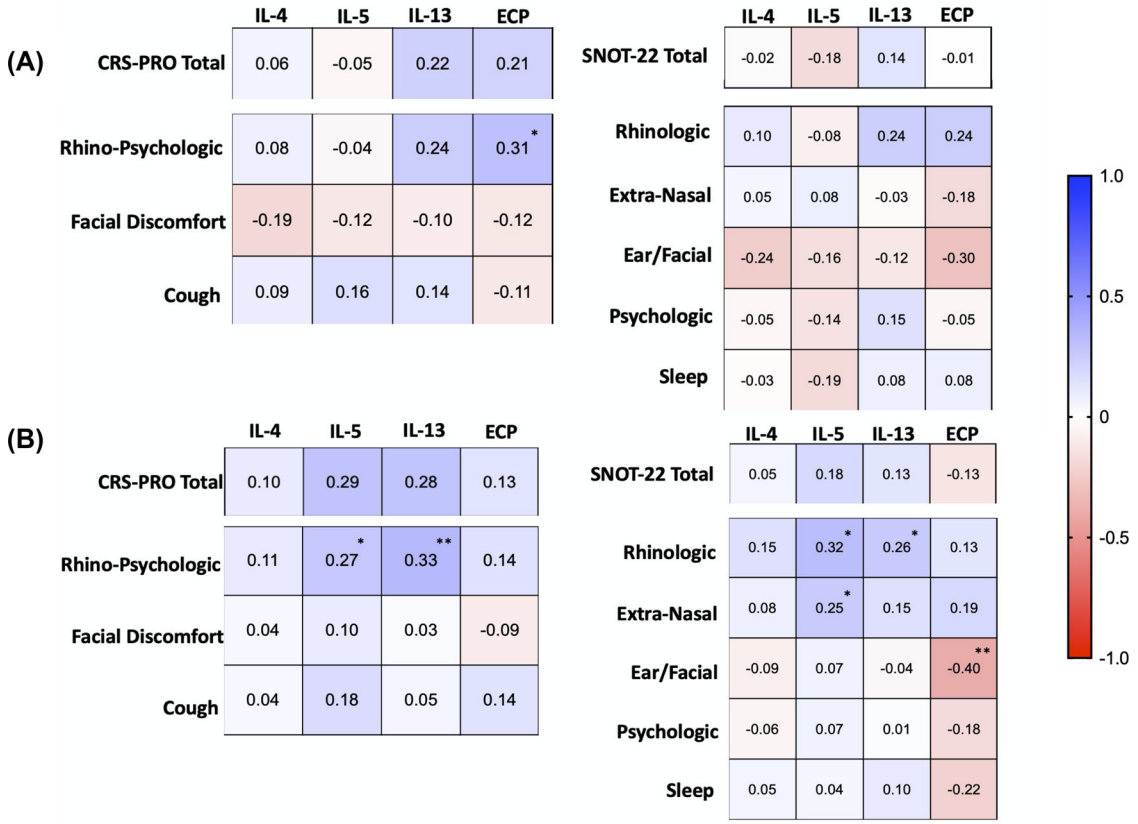

FIGURE 3 CRSsNP cohort correlation between type 2 mediators and the CRS-PRO (A) pre-ESS and (B) post-ESS Spearman correlation coefficients between contemporaneous middle mucus cytokine measures with the PROM total score and their individual subdomains in heatmap format. Blue gradient: positive correlation; red gradient: negative correlation. Spearman correlation *r* values depicted in center of corresponding boxes ($^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$). CRS-PRO = CRS-PRO = 12-item Chronic Rhinosinusitis-Patient Reported Oucome,; CRSsNP = CRS without nasal polyps; ESS = endoscopic sinus surgery; PROM = patient-reported outcome measurement

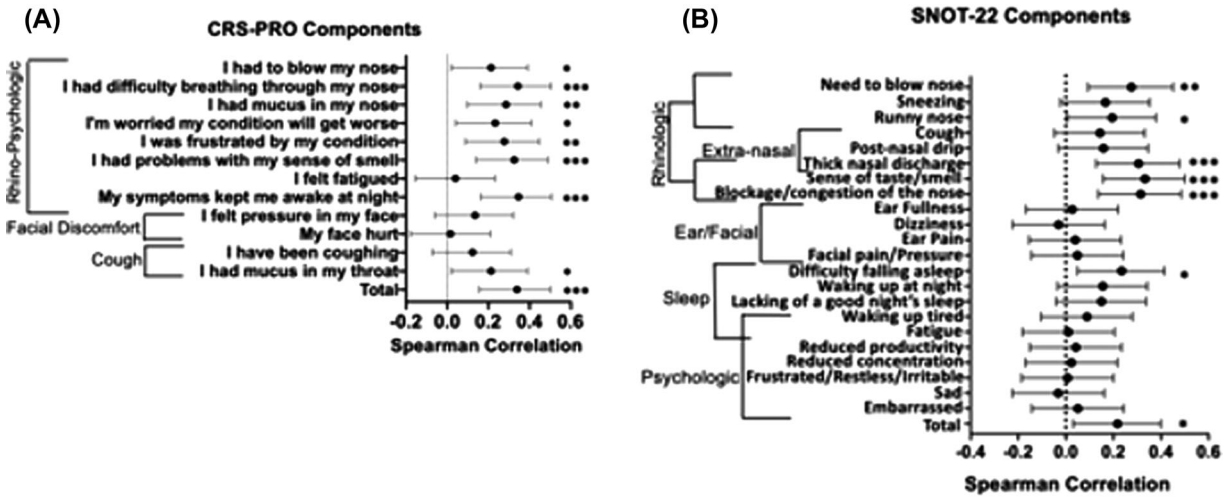

FIGURE 4 Individual question correlations of CRS-PRO and SNOT-22 with post-ESS mucus levels of IL-13 in entire cohort of patients. (A) CRS-PRO and (B) SNOT-22 correlation of total cohort with each individual question of the PROMs forest plot with 95% confidence interval. Spearman correlations ($^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$). CRS-PRO = CRS-PRO = 12-item Chronic Rhinosinusitis-Patient Reported Oucome,; ESS = endoscopic sinus surgery; PROM = patient-reported outcome measurement; SNOT-22 = 22-item Sino-Nasal Outcome Test

into "high" or "low" cytokine levels determined via a clustering algorithm and found that total SNOT-22 score was significantly higher in the "high IL-13" vs the "low IL-13" group.[29] Our findings are in concordance with their studies finding that the SNOT-22 or CRS-PRO total score did not correlate with T2 inflammation, with the exception of IL-4 pre-ESS in CRSwNP patients.

In contrast to the earlier studies, we had ability to assess correlation of PROMs with T2 biomarkers both before and after ESS, and we noted an intriguing divergence in their correlations in the 2 periods. Although there were few to no correlations between any of the instruments' total scores with T2 inflammation pre-ESS, the post-ESS period revealed much stronger correlations between the CRS-PRO and T2 inflammation intensity among all CRS patients, but especially among those with CRSwNP, particularly when measured using the CRS-PRO. Although the CRSsNP subgroup showed no correlation between PROM total scores and T2 inflammation post-ESS, certain domains, like the rhinopsychologic subdomain of the CRS-PRO and the SNOT-22 rhinologic subdomain, appeared to consistently reflect residual T2 inflammation, even among patients with CRSsNP. One reason why symptomatic severity has a better correlation with T2 biomarkers in the post-ESS period could be due to the patient and physician selection of patients undergoing ESS. Because few patients with minimal symptom burden pursue ESS, correlations in that time period lacked a correlational anchor, whereas many patients whose inflammation resolves after ESS also have a minimal T2 inflammation burden. Nonetheless, these findings suggest clinicians should recognize that post-ESS residual symptom burden measured by the CRS-PRO, especially the symptoms that comprise the CRS-PRO rhinopsychologic domain, may have a relationship with underlying T2-inflammation burden—a relationship not seen by previous studies. We do acknowledge the described level of correlation between PROMs and inflammatory mediators is generally weak to moderate, depending on mediator and instrument or subdomain, but relationships between biomarkers and patient-reported severity are weak to nonexistent across a variety of human conditions.[30,31]

We also noted that the correlation of T2-inflammatory cytokines and either PROM was better among CRSwNP patients when compared with CRSsNP patients. This may be reflective of evidence that T2 inflammation is the dominant type of inflammation found in most Western CRSwNP patients and thus is a less heterogeneous disease with symptom severity primarily reflecting T2 severity.[4–6] This relationship was also seen in previous work that categorized CRS patients into either Th2 high or low groups based on measurement on IL-4, IL-5, and IL-13, with the Th2 high group being characterized by higher symptom scores on SNOT-22.[29] The lack of a correlation in CRSsNP patients' PROMs and T2 mediators pre- and post-ESS may reflect the underlying heterogeneity of the inflammatory processes that drive CRSsNP, resulting in other inflammatory processes that drive CRSsNP symptom burden.[7]

PROMs for individual conditions are frequently comprised of different domains, which are identified via coordinate responses to individual symptom items. In our earlier analysis, the first and largest subdomain of the CRS-PRO was the rhinopsychologic domain, which comprised both rhinologic symptoms and the psychologic impact of CRS. On the SNOT-22, DeConde et al identified the rhinologic subdomain of the SNOT-22 as its first domain followed by the extranasal symptom subdomain.[24] We found the CRS-PRO rhinopsychologic and SNOT-22 rhinologic domains to be particularly correlated with T2 inflammation in each cohort regardless of timing pre- or post-ESS. This may be expected as these are the subdomains in each instrument that address 3 of the 4 cardinal symptoms of CRS. Given tissue eosinophilia has been found to correlate with olfactory loss there is a logical connection between the correlation of these subdomains with T2-inflammatory mediators.[32] In contrast to the SNOT-22 rhinologic domain, the rhinopsychologic subdomain of the CRS-PRO, which also includes items on psychologic impact and sleep interruption, maintained a correlation with T2 biomarkers, unlike the corresponding psychologic and sleep subdomains of the SNOT-22. For example, in our limited individual symptom analysis correlation with post-ESS IL-13 (Fig. 4), we found that only CRS-PRO's sleep item "My symptoms kept me awake at night" was highly significantly correlated with IL-13, whereas the SNOT-22's "Difficulty falling asleep" item had weaker correlations and "Waking up at night," "Lacking of a good night's sleep," and "Waking up tired" did not. We believe the brevity of the CRS-PRO instrument, which was distilled using extensive patient input,[21,22] allows the instrument to capture extrarhinologic effects that are most pertinent to T2 inflammation.

We recognize that our study is limited due to the use of mucus rather than tissue, which is the method traditionally used to measure inflammatory markers. Many correlations calculated during the exploratory (subdomain/individual items) phase of this study were not evaluated with multiple testing correction analyses. However, for these exploratory analyses, we only discussed items that repeatedly had correlation with T2 biomarkers across phenotypes and timing of assessment or items from specific subdomains that repeatedly showed correlation, which minimizes the likelihood of type I error. In addition, our patient cohort included patients undergoing revision ESS and with varying degrees of surgical intervention. Intra- and post-ESS medical management was not standardized

TABLE 2 Post-ESS medical treatment[a]

	CRSsNP (n = 71)	CRSwNP (n = 52)	*p*Value
Propel placement	31 (44%)	38 (73%)	0.001
Enhanced topical steroid	29 (41%)	44 (85%)	<0.001
Standard INCS	29 (41%)	9 (17%)	0.005
Nasal antihistamine	14 (20%)	2 (4%)	0.01
Biologic	1 (1%)	5 (10%)	0.01
Systemic antibiotics	12 (17%)	9 (17%)	0.95

[a]Data expressed as number (%). Enhanced topical steroid includes budesonide/mometasone rinses or drops and Xhance INCS.
CRSsNP = CRS without nasal polyps; CRSwNP = CRS with nasal polyps; ESS = endoscopic sinus surgery; INCS = inhaled nasal corticosteroids; SNOT-22 = 22-item Sino-Nasal Outcome Test.

and was left up to individual surgeon discretion (Table 2). Measurement of cytokine levels was done once rather than in duplicate due to the low volume of mucus collected from each patient. Pre-ESS PROMs were not universally available from every patient, although the majority (78%) did have these data available. Nevertheless, our study is the first to compare the correlation of T2 inflammatory markers with well-validated measures of CRS—the CRS-PRO and the SNOT-22—with a direct comparison of each.

5 | CONCLUSION

The CRS-PRO has a stronger correlation to T2 inflammatory mediators in CRS as a total instrument as well as to greater individual components compared with the SNOT-22.

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