

Atopy in chronic rhinosinusitis: impact on quality of life outcomes

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Background: Chronic rhinosinusitis (CRS), in particular with nasal polyps (CRSwNP), has been linked with skewed T-helper 2 and immunoglobulin E (IgE)-mediated allergic responses. The role of atopy in CRS, however, remains unclear. Correlations between immunological allergic markers and patient-reported outcomes measures (PROMs) were investigated.

Methods: A cross-sectional study of adult patients with CRS undergoing endoscopic sinus surgery was conducted. Immunological allergic markers included automated immunoassay testing for serum-specific IgE to common allergens (house dust mite, grass, mold, animal epithelia) and total IgE. PROMs were assessed using the 22-item Sino-Nasal Outcome Test (SNOT-22). Patients were defined as atopic based on either a positive specific IgE or elevated total IgE (>160 kU/L).

Results: A total of 446 patients (45.7% female, age 49.05 ± 14.96 years) were recruited, of which 42.8% had asthma, 51.6% had CRSwNP, and 63.0% had eosinophilic CRS. Positive allergen sensitization was detected in 52.9% patients. Total IgE levels were elevated in 28.0% with mean IgE level of 161 ± 269 kU/L. Atopy was associated with younger age at the time of surgery, CRSwNP, asthma, and eosinophilic CRS

(eCRS). Atopy was also associated with increased severity in nasal symptom score (13.1 ± 6.4 vs 11.9 ± 6.0 , $p = 0.04$), as well as worse scores in the loss of smell/taste ($\chi^2(1) = 5.97$, $p = 0.02$) and need to blow nose ($\chi^2(1) = 4.26$, $p = 0.04$) questions in the CRS population. In the CRSwNP population, there was no significant association between atopy and PROMs.

Conclusion: Comorbid atopy in CRS is associated with additional symptom burden, reflected mainly within the nasal symptom quality of life markers. Atopy assessment in CRS is important to ensure appropriate and successful treatment of the disease. © 2018 ARS-AAOA, LLC.

Key Words:

atopy; allergy; chronic rhinosinusitis; patient-reported outcome measures; quality of life; nasal polyps; immunoglobulin E; ImmunoCAP

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Chronic rhinosinusitis (CRS) is a heterogeneous disease characterized by inflammation of the paranasal sinuses with different disease subtypes. It is associated with a significant impact on quality of life (QoL) and accompanying financial burden, representing a leading cause of absenteeism and lost productivity within the workplace.¹ In Europe, the prevalence of CRS is 10.9% based on the European Position Paper on Rhinosinusitis and Nasal Polyps (EP3OS) diagnostic criteria.²

Atopy is characterized by the production of specific immunoglobulin E (IgE) antibodies in response to allergens. In some CRS studies, the term atopy or allergy may often be used interchangeably with allergic rhinitis, rather than describing a truly atopic population with demonstrated atopic testing. The role of atopy in CRS remains unclear, with conflicting evidence existing within the literature.^{3,4}

There are 2 theories regarding the relationship between the atopy and CRS: (1) atopy may be a disease-modifying factor in the inflammatory process of CRS, or (2) atopy may simply be a comorbidity affecting the same end organ, thus

adding to the symptom burden. Continuing exposure to allergens may lead to an ongoing late-phase inflammatory response that may lead to the chronic airway symptoms in CRS, as well as asthma.^{5,6}

CRS with nasal polyps (CRSwNP) and eosinophilic CRS (eCRS) have been linked with a skewed T-helper 2 (Th2) response, a response mediated by Th2 cytokines that promotes the production of IgE and eosinophilic inflammation. Local, rather than systemic IgE, is thought to be responsible for the inflammatory process in CRSwNP and eCRS. Total IgE and the number of IgE-positive cells in tissue have been shown to be elevated in the nasal polyp tissue in patients with eCRS compared with non-eCRS.⁷ Additionally, raised total IgE in nasal polyps is significantly associated with elevated interleukin 5 (IL-5) and eosinophil cationic protein levels, implying a correlation between IgE and eosinophilic inflammation. It is proposed that this is due to a local class switching to IgE and local IgE production, rather than derived from the systemic circulation.⁸ Total serum IgE, positive skin-prick testing (SPT), or immunoassay testing for serum-specific IgE have previously shown no significant association with elevated tissue IgE.⁷⁻¹⁰

This study investigates the potential association between systemic immunological atopic markers and reported QoL within the CRS population.

Materials and methods

A cross-sectional study of patients undergoing functional endoscopic sinus surgery (FESS) at Macquarie University and St Vincent's Hospital was performed. This study had ethical approval from the St Vincent's Hospital Human Research Ethics Committee (SVH 09/083), and patients provided informed consent for research data collection.

Consecutive adult patients (≥ 18 years) seen at a tertiary referral clinic, who were diagnosed with CRS, failed medical therapy (according to EP3OS), and underwent FESS as part of the management for their disease, were included in the study. These patients had ceased all systemic corticosteroid medication for at least 4 weeks prior to surgery.

Patients with established immunodeficiency, coagulation disorder, pregnancy, classic allergic fungal sinusitis, cystic fibrosis, oral corticosteroid use in the previous 4 weeks, previous omalizumab use, or previous treatment with immunotherapy were excluded from the study.

Demographic characteristics were recorded, including patient age, gender, asthma, and previous surgery. Asthma status was determined based on historical data provided by the patient (either a 15% change in forced expiratory volume in 1 second (FEV1) on spirometry results on challenge testing or β -agonist use or if actively using regular active and/or preventer medication for asthma). The presence of nasal polyps was confirmed with an endoscopic examination. Previous CRS surgery was defined as any previous procedure as surgical intervention for CRS, and thus, now undergoing a revision operation.

Assessment of eCRS

Sinus mucosal specimens were obtained intraoperatively and placed in formalin. These were then processed with standard hematoxylin and eosin (H&E) staining and assessed by pathologists blinded to the clinical data. eCRS was defined by histopathological assessment showing more than 10 eosinophils/high-power field (HPF) (magnification $\times 400$) on 2 separate HPFs.¹¹

Assessment of atopic status

A preoperative blood sample was taken and assessed for total blood eosinophil count ($\times 10^9/L$), eosinophil to white cell count (WCC) percentage (%), and automated immunoassay testing by ImmunoCAP (Phadia Laboratory Systems, Uppsala, Sweden) for total IgE (kU/L) and specific IgE antibodies to common allergens (house dust mite mix, grass mix, mold mix, animal epithelia mix) (kUa/L). The house dust allergen mix tested for IgE to *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, and *Blattella germanica*. The grass mix tested for IgE to *Anthoxanthum odoratum*, *Cynodon dactylon*, *Lolium perenne*, *Phleum pratense*, and *Sorghum halepense*. The mold mix tested for IgE to *Penicillium notatum*, *Cladosporium herbarum*, *Aspergillus fumigatus*, and *Alternaria tenuis*. The epithelial mix tested for IgE to cat, horse, cow, and dog dander. Positive atopic status was defined as either elevated total IgE (>160 kU/L) or any positive ImmunoCAP test for allergen-specific IgE (>0.35 kU/L). Additionally, because of the known seasonality of grass allergy, the population of grass-sensitive patients was divided into 2 groups based on the timing of the 22-item Sino-Nasal Outcome Test (SNOT-22) completion. The seasonal grass-sensitive population was defined by a SNOT-22 completed between September 1 and December 31 and a nonseasonal grass-sensitive population at other times. All parameters were assessed in a blinded fashion.

Patient-reported outcome measures

As patient-reported outcomes measures (PROMs), each patient completed a preoperative SNOT-22, a validated disease-specific QoL assessment.¹² The results from the SNOT-22 were used to determine separate QoL domains, including a nasal symptom score (NSS), rhinologic symptoms, extranasal rhinologic symptoms, ear/facial symptoms, sleep dysfunction, and psychological dysfunction. The components of these scores have been described.^{12,13}

Statistical analysis

Comparisons between atopic and nonatopic groups were performed. Statistical analysis was conducted using SPSS Statistics version 22 (IBM Corp., Armonk, NY). Parametric results were expressed as mean $\pm$ 1 standard deviation (SD). Linear-by-linear association chi-square test was utilized for the analysis of individual SNOT-22 score components against atopy. Independent samples *t* test was utilized for continuous data, including total SNOT-22 score

TABLE 1. Baseline characteristics (n = 336)

Characteristic	Value
Age at time of surgery (years), mean $\pm$ SD	49.05 $\pm$ 14.96
Gender (female), %	45.7
Asthma, %	42.8
Presence of nasal polyps (CRSwNP), %	48.4
Prior surgery, %	48.7
Eosinophilic CRS, %	63.0
Immunoassay specific-IgE positive, %	52.9
House dust mite	34.1
Grass mix	33.6
Mold mix	13.5
Animal epithelia mix	13.9
IgE raised (>160 kU/L), %	28.0
IgE (kU/L), mean $\pm$ SD	161 $\pm$ 269
Atopic (%)	59.9

CRS = chronic rhinosinusitis; CRSwNP = CRS with nasal polyps; IgE = immunoglobulin E.

and SNOT-22 subdomain analysis. All *p* values were 2-tailed and a value of *p* < 0.05 was considered statistically significant.

Results

A total of 446 patients (45.7% female, age 49.05 $\pm$ 14.96 years) were recruited, of which 42.8% had asthma, 48.4% had CRSwNP, and 63.0% had eCRS (Table 1).

Allergen sensitization by specific serum IgE to 1 or more allergen groups was detected in 52.9% of patients. Of those, the majority of patients showed elevated specific IgE to dust mix (64.4%) and grass mix (63.6%). A total of 53.4% of sensitized patients were polysensitized; ie, demonstrated sensitivity to 2 or more allergen groups. Of the 150 grass-sensitized patients, 29.3% answered their SNOT-22 during the spring seasonal period and were considered seasonal grass-sensitized. Total serum IgE levels were elevated in 125 patients (28%), with overall mean of 161 $\pm$ 269 kU/L. Overall, 267 patients (59.9%) were deemed atopic.

Allergen sensitization relationship to disease characteristics

When comparing baseline characteristics of the atopic and nonatopic patients, patients with atopy were found to be younger at the time of surgery (47.80 $\pm$ 14.21 vs 50.91 $\pm$ 15.86 years, *p* = 0.03), as well as more likely to have CRSwNP ($\chi^2(1) = 4.27$, *p* = 0.04), asthma ($\chi^2(1) = 8.19$, *p* < 0.01), and eCRS ($\chi^2(1) = 11.27$, *p* < 0.01) (Table 2).

Patients with positive allergen sensitization presented higher eosinophil counts (0.36 $\pm$ 0.30 $\times 10^9$ /L vs 0.25 $\pm$ 0.24 $\times 10^9$ /L; *p* < 0.01) and eosinophil to WCC% (5.23 $\pm$ 4.15% vs 3.80 $\pm$ 3.28%, *p* < 0.01). Allergen sensitization to grasses ($\chi^2(1) = 5.68$, *p* = 0.02), mold ($\chi^2(1) = 6.81$, *p* < 0.01), and epithelial mix ($\chi^2(1) = 8.53$, *p* < 0.01) was associated with increased likelihood of asthma. Allergen sensitization to dust mite was not associated with asthma ($\chi^2(1) = 0.62$, *p* = 0.43).

Allergen sensitization relationship to PROMs

There was no significant association between allergen sensitization and patients' overall SNOT-22 score (44.4 $\pm$ 23.4 vs 42.6 $\pm$ 21.6, *p* = 0.42). However, atopy was associated with increased severity in the NSS (13.1 $\pm$ 6.4 vs 11.9 $\pm$ 6.0, *p* = 0.04) (Fig. 1). Atopic patients also demonstrated higher severity in the loss of smell/taste ($\chi^2(1) = 5.97$, *p* = 0.02) and need to blow nose ($\chi^2(1) = 4.26$, *p* = 0.04) questions. There were no associations with other questions in the SNOT-22 questionnaire (data not shown).

Serum IgE to PROMs

Raised total IgE was associated with increased severity in the NSS (13.8 $\pm$ 6.3 vs 12.2 $\pm$ 6.2, *p* = 0.02) and SNOT-22 rhinologic subset (18.3 $\pm$ 8.3 vs 16.4 $\pm$ 8.7, *p* = 0.04) (Fig. 2), as well as poorer scores in the cough ($\chi^2(1) = 5.77$, *p* = 0.02) and loss of smell/taste questions ($\chi^2(1) = 7.85$, *p* < 0.01).

CRSwNP

Allergen sensitization relationship to disease characteristics within the CRSwNP subset

Within the CRSwNP population, allergen sensitization was associated with elevated total blood eosinophil count (0.46 $\pm$ 0.34 $\times 10^9$ vs 0.33 $\pm$ 0.26 $\times 10^9$, *p* < 0.01) and eosinophil to WCC% (6.57 $\pm$ 4.54% vs 4.95 $\pm$ 3.80%, *p* < 0.01). There was no association with age (49.41 $\pm$ 13.54 vs 51.78 $\pm$ 13.95 years, *p* = 0.23).

Allergen sensitization relationship to PROMs within the CRSwNP subset

There was no association between atopy in the CRSwNP population and SNOT-22 score, in terms of both total score (47.2 $\pm$ 25.5 vs 46.1 $\pm$ 25.5, *p* = 0.76), subdomains, and individual questions (data not shown).

eCRS

Allergen sensitization relationship to disease characteristics within the eCRS subset

Within the eCRS population, allergen sensitization was associated with elevated total blood eosinophil count (0.43 $\pm$ 0.33 $\times 10^9$ /L vs 0.35 $\pm$ 0.28 $\times 10^9$ /L, *p* = 0.04). There was no association with age (47.96 $\pm$ 13.71 vs 51.28 $\pm$ 13.87 years, *p* = 0.06) or eosinophil to WCC% (6.24 $\pm$ 4.45% vs 5.21 $\pm$ 3.68%, *p* = 0.052).

TABLE 2. Atopic status and disease characteristics

Characteristic	Atopic (n = 267)	Nonatopic (n = 179)	p
Age at time of surgery (years), mean $\pm$ SD	47.80 $\pm$ 14.21	50.92 $\pm$ 15.86	0.03
Gender (female), %	43.4	49.2	0.24
Asthma, %	48.3	34.6	<0.01
Presence of nasal polyps (CRSwNP), %	52.4	42.5	0.04
Prior surgery, %	47.6	50.3	0.57
Eosinophilic CRS, %	69.3	53.6	<0.01

CRS = chronic rhinosinusitis; CRSwNP = CRS with nasal polyps; SD = standard deviation.

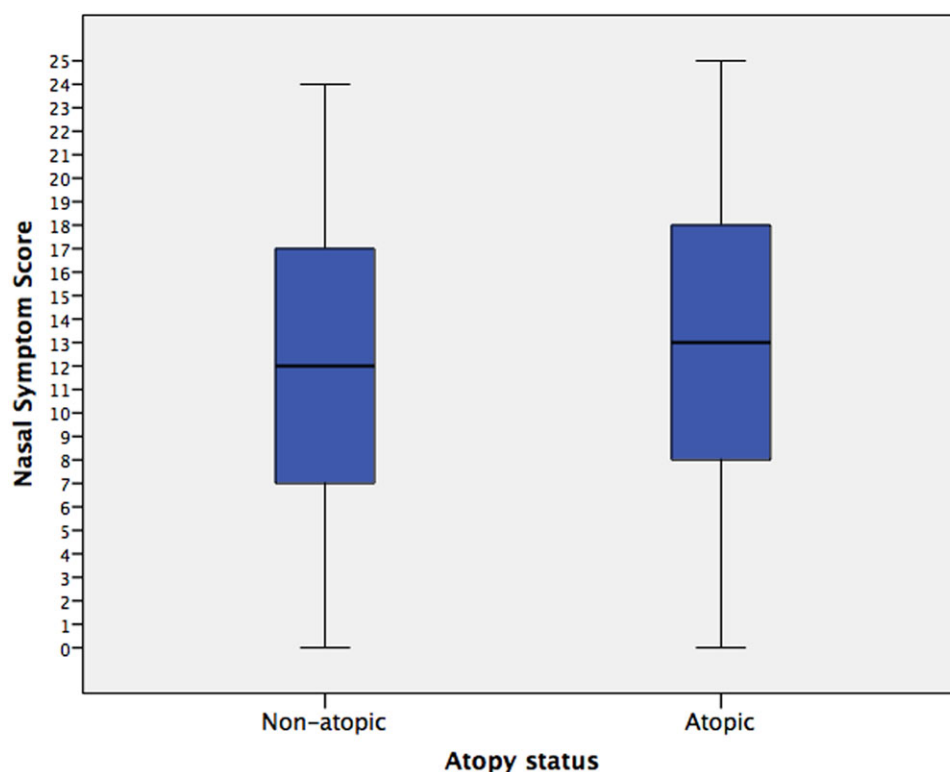


FIGURE 1. Comparison of nasal symptom score between atopic and nonatopic patients. Patients were divided into atopic and nonatopic groups based on either elevated total IgE (>160 kU/L) or any positive ImmunoCAP test for allergen-specific IgE (>0.35 kU/L). Results are represented with box plots of median, 25th and 75th percentiles, and 5th and 95th percentile whiskers. Statistical analysis was performed using Independent samples t test. IgE = immunoglobulin E.

Allergen sensitization relationship to PROMs within the eCRS subset

In the eCRS with atopy population, the need to blow nose score was significantly greater than the nonatopic eCRS group ($\chi^2(1) = 4.52$, $p = 0.03$). There was no association with overall SNOT-22 score ($p = 0.70$), subdomains, or other individual components (data not shown).

Seasonality of grass allergen sensitization

The grass-sensitive CRS population within the known seasonal allergy period (September to December) showed more severe scores in need to blow nose ($\chi^2(1) = 4.16$, $p = 0.04$), sneezing ($\chi^2(1) = 3.90$, $p = 0.048$), and ear pain subsets

($\chi^2(1) = 5.43$, $p = 0.02$) than those outside the seasonal allergy period. Although this was not associated with the overall SNOT-22 score (51.18 ± 25.42 vs 43.29 ± 22.89 , $p = 0.07$), the seasonal grass-sensitized CRS population had more severe scores in NSS (15.39 ± 6.12 vs 13.13 ± 6.37 , $p = 0.048$) and SNOT-22 rhinologic subset (20.27 ± 8.32 vs 17.02 ± 8.86 , $p = 0.04$).

Discussion

In this study, atopy was associated with increased severity in certain aspects of a CRS patient's QoL but no significant change in overall score. Although atopy itself may not contribute directly to the pathogenesis of CRS, it may

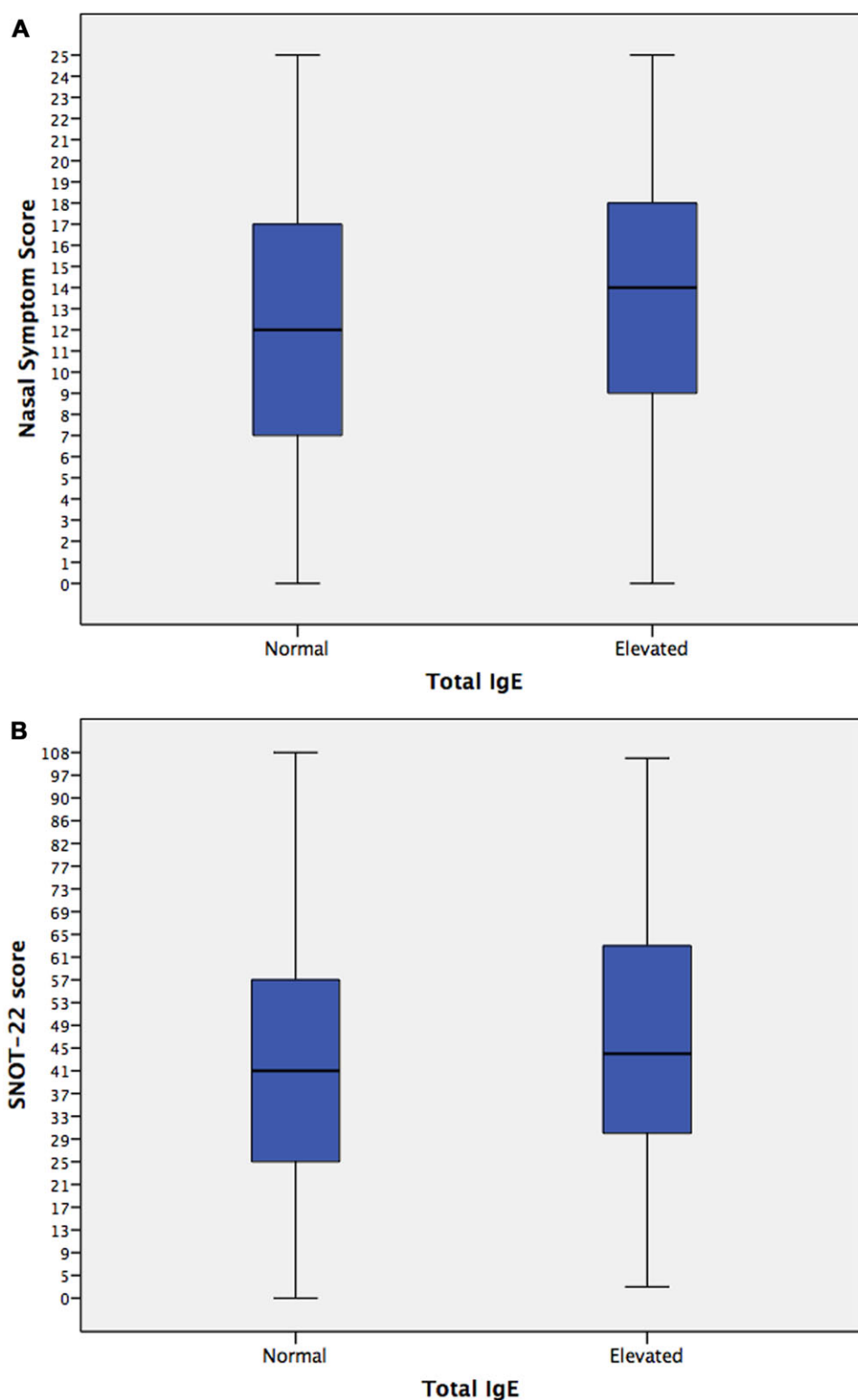


FIGURE 2. Comparison of (A) nasal symptom score and (B) SNOT-22 rhinologic subset between patients with normal and elevated total IgE levels. Patients were divided into elevated and non-elevated total serum IgE groups based on a cutoff of 160 kU/L. Results are represented with box plots of median, 25th and 75th percentiles, and 5th and 95th percentile whiskers. Statistical analysis was performed using independent samples t test. IgE = immunoglobulin E; SNOT-22 = 22-item Sino-Nasal Outcome Test.

contribute to a disease-modifying role in CRS or may be two coexistent diseases.

Atopy was found to be associated with increased severity in the total NSS, as well as higher severity in the loss of smell/taste and need to blow nose subsets. Because atopic patients are classically more likely to have allergic rhinitis, the worsening of nasal symptoms (need to blow nose, sneezing, runny nose, loss of smell/taste) may reflect a manifestation of allergic rhinitis symptoms within these patients. Patients with raised total IgE, with or without specific IgE sensitization, showed additional severity in the SNOT-22 rhinologic domains, as well as the cough question, which may reflect a potentially more systemic effect of IgE in this population.

Although there was a limited effect of atopy on CRS overall QoL, the presence of nasal polyps provided a more appreciable effect on patient symptoms. CRSwNP has been previously associated with poorer outcomes and decreased QoL.^{14,15} On further analysis of the CRSwNP population, there was no significant association between atopy and QoL measures. Thus, the presence of atopy in CRSwNP appears to have no significant impact on the symptom burden of CRSwNP. In the eCRS population, only the need to blow nose subset was significantly worse in the atopic group than the nonatopic population. Interestingly, Alobid et al.¹⁶ showed that in a group of patients with severe nasal polyposis, atopic patients (based on SPT) had worse QoL than nonatopic patients, in the physical and mental components of the 36-Item Short Form Health Survey (SF-36).

Some studies have assessed the association between atopy and CRS QoL based on SPT. Allergists often prefer SPT because it is more sensitive than serum-specific IgE and the result is available at the time of consultation so that clinical decisions can be made immediately. However, in the present study, atopy was measured based on serum-specific IgE. This is reflective of investigations which have shown that this assessment of atopy is more precise and quantitatively accurate than SPT, and allows for greater assessment of sensitization and comparison between patients.¹⁷⁻¹⁹

Not unsurprisingly, in the grass-sensitized population who answered their SNOT-22 questionnaires during the spring seasonal period, we found poorer scores in the need to blow nose, sneezing, and ear pain questions. They also had increased severity in the NSS and SNOT-22 rhinologic subset, reflecting that symptoms of comorbid allergic rhinitis may worsen during seasonal times. Further comparison of seasonal and nonseasonal PROMs in this grass-sensitized population may be useful to determine the effect of seasonality.

Atopic patients were more likely to undergo surgical intervention at a younger age. This may be because these patients were more likely to fail maximal medical management for their CRS at an earlier stage than nonatopic patients, thus seeking surgical intervention sooner. However, there was no association between atopy and likelihood of revision surgery.

The strength of this study lies within its large sample size and analysis of atopy based on both specific and total IgE levels. However, it is important to note that the populations included within this study have all failed medical therapy and require surgical management of their CRS, and thus, may represent those with more severe disease.

To be comprehensive, PROMs should be evaluated in conjunction with clinical features, endoscopy findings, laboratory markers, and radiographic scans. Further evaluation of atopy based on local mediators would be useful to identify local factors in conjunction with systemic factors, which may influence QoL outcomes. Radiologic associations were not assessed within this study. However, previous investigations have shown that allergy is associated with increased CRS severity based on computed tomography (CT) imaging as measured by the Lund-Mackay score.²⁰ Central compartment atopic disease (CCAD) refers to a pathological finding of middle turbinate edema, secondary to aeroallergen sensitisation.²¹ CCAD based on radiologic pattern has been recently identified as significantly associated with inhalant allergen sensitization; however, there were no significant associations between CCAD phenotype and QoL.²²

Targeted treatment of CRS patients with atopy is important in improving patients' control of their symptoms and overall QoL. Omalizumab is an anti-IgE monoclonal antibody that has been investigated in CRS with nasal polyps; although it has been shown to be effective in both atopic and nonatopic patients (n = 24), further data with a larger study sample are required to more accurately assess its usefulness in CRS with atopy and other upper airway diseases in the future.²³⁻²⁵

Conclusion

Comorbid atopy in CRS leads to an additional symptom burden within these patients, reflected mainly within the nasal symptom subsets of the SNOT-22. However, it did not significantly worsen QoL in the CRSwNP population. In treating patients with CRS, it is important to carefully assess for atopy and institute appropriate management to ensure successful treatment of the disease. 

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