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Dana L. Crosby Date

Impact of age on outcomes following endoscopic sinus surgery for chronic rhinosinusitis

By

Dana Crosby, MD
MPH, Emory University, 2018
Applied Epidemiology

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Executive Master of Public Health
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Dana L. Crosby, MD

ABSTRACT

Background: Chronic rhinosinusitis (CRS) is a common condition, which affects people of all ages and has a dramatic negative impact on quality of life (QOL). There are many factors that can impact CRS outcomes following Endoscopic Sinus Surgery (ESS) to treat CRS. The goal of this study is to determine if there are differences in outcomes by age group following ESS for CRS utilizing preoperative and postoperative 22-item Sino-Nasal Outcome Test (SNOT-22) scores.

Methods: Data from 1,252 adult CRS patients electing to undergo ESS (2007-2018) were collected retrospectively. The median age of 50 was used to divide the data into two groups for comparison of the impact of age on SNOT-22 scores at each time point including preoperative, three, six and twelve months after surgery. Changes of SNOT-22 scores were analyzed using a mixed models analysis in order to determine the effect of age.

Results: The mean age of patients was 48.6 years. Males comprised 55.2% of the patients and most patients were white (87.0%). Polyps were present in 53.9% of patients. Mean SNOT-22 score was 41.0 and was higher in patients younger than 50 years old compared to those of at least 50 years of age. After adjusting for gender, race, polyp status, and number of prior ESS, patients younger than 50 had a higher mean pre-ESS SNOT-22 score (44.0) compared to those of at least 50 years of age (38.9). Among patients younger than 50, SNOT-22 scores declined by 20.7 points at 3 months post-ESS and 16.1 points at 6 months post-ESS. The rate of change between the dichotomized age groups was not significantly different at 3 and 6 months post-ESS ($p = 0.7952$ and $p = 0.1057$, respectively).

Conclusions: Both age groups showed significant and durable improvement in SNOT-22 scores after ESS. Patients younger than 50 years of age have higher pre-ESS SNOT-22 scores, but converge to have the same SNOT-22 scores at three and six months post-ESS. The rate of change of SNOT-22 scores at three and six months is not different between those younger than 50 years and those of at least 50 years.

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CHAPTER I: INTRODUCTION

Chronic rhinosinusitis (CRS) is a common medical condition that is defined as an inflammatory process affecting the sinonasal mucosa for at least 12 consecutive weeks. According to the most recent update by the CRS task force, CRS is defined as 12 weeks or longer of two or more of the following signs or symptoms: mucopurulent drainage, nasal obstruction, facial pain, or decreased sense of smell.[1] In addition to these signs and symptoms, the diagnosis of CRS requires identification of inflammation documented by at least one of the following objective measures: purulent mucus or edema in the middle meatus or anterior ethmoid region, polyps, or radiographic imaging showing inflammation of the paranasal sinuses. Relying solely on patient reported symptoms is an unacceptable method of diagnosis given its very poor specificity. Therefore, objective evidence of inflammation of the sinonasal mucosa via nasal endoscopy or radiographic imaging is required for diagnosis.

CRS has a highly varied clinical presentation, histopathology, and pathophysiology. Given the diversity of this disease process, CRS is best thought of as a complex of systems that represents a common endpoint of a variety of inflammatory disease processes affecting the sinonasal cavity. Over the years, CRS has been divided into subtypes in a variety of ways. The most common distinction in the literature divides CRS into two groups based on the presence or absence of sinonasal polyposis. These two subtypes are thus known as chronic rhinosinusitis with nasal polyps (CRSwNP) and chronic rhinosinusitis without nasal polyps (CRSsNP). There are significant differences in symptomatology, pathophysiology, and treatment between these two disease processes.

The pathophysiology of CRS is still poorly understood, but is generally stated as any process that leads to the common endpoint of inflammation of the sinonasal mucosa.[2] It is believed that host factors, including adaptive and innate immunity, interact with environmental factors in such a way to lead to an inflammatory response within the paranasal sinuses. It has proved very difficult to tease out which cellular and inflammatory mediators are causative of the inflammatory process and which are in response to the inflammatory process. Both CRSwNP and CRSsNP display cellular infiltrates and proinflammatory cytokines. While the cellular and molecular mediators are inconsistent even within the two subtypes, some generalizations can be made. Analysis of tissue from nasal polyps more commonly shows an eosinophilic infiltrate, histamine, interleukin-5 (IL-5) and interleuken-13 (IL-13) with a Type 2 helper cells (Th2) biased cytokine profile.[3] In the setting of CRSsNP neutrophilic infiltration often predominates.[4] Unfortunately, these designations are not clear-cut and the lines are often blurred due to heterogeneity even within subtypes of CRS. Regardless of the cause, the inflammatory state of the paranasal sinuses leads to poor mucociliary function and accumulation of thickened secretions.

Throughout the study of CRS many environmental and microbial stimuli have been implicated in the etiology of this disease process. Superantigens, biofilms, and fungus all had their time in the spotlight as *the cause* of CRS. Tobacco smoke and environmental irritants have also been implicated.[4-6] Unfortunately, the more that is learned about CRS, the more it seems unlikely that there is one sole cause that will be the key to understanding this disease process. Instead, all of these factors as well as many others are all likely to contribute to this condition.

CRS affects all age groups and is one of the most common chronic disease processes in developed nations with a prevalence of 5 – 12% in North America and Europe. [7-9] It is reported that each year approximately 18 million physician visits are due to CRS in the United States.[10] CRS with and without nasal polyposis is present in all racial groups. However, it has been reported that there is unequal access to specialists and treatments, potentially leading to differential underestimates of prevalence in some racial groups. It was shown that white patients were more likely to have seen a specialist regarding their sinus symptoms and were more likely to have undergone surgical intervention compared African Americans, Hispanics, and Asians. Additionally, African Americans and Hispanics were more likely to delay access to medical care for their sinuses due to cost concerns.[11]

Unfortunately, epidemiologic data for CRS remains scarce and often conflicting. Those affected by CRS have a significant decrease in quality of life (QOL) measures. Using the Medical Outcome Study Short-form 36, patients with CRS had a significant decrease in measures of bodily pain, general health, vitality, and social functioning. [12] Scores for both social functioning and bodily pain were significantly worse for patients with CRS compared to patients with other chronic diseases such as congestive heart failure, chronic obstructive pulmonary disease, and chronic back pain.

In addition to the health burden suffered by patients who live with CRS, there is a significant financial burden as well. In a review of the literature of the cost of adult CRS it was noted that the direct CRS-related healthcare cost ranged from 6.9 to 9.9 billion dollars per year.[13] Indirect costs associated with missed days of work and loss of

productivity exceed 13 billion dollars annually. The overall annual economic burden of CRS each year in the United States was found to be approximately 22 billion dollars.

On an individual level it has been shown that the mean number of lost work days for a patient with CRS was 24.6 days per year. Similarly, it was shown that 21.2 household days were lost per patient annually.[14] Household days were considered to be 7 hours on a weekday and 15 hours on weekend day. Patients were asked how much of this time was spent caring for their sinuses per day. Therefore, if a patient spent 7 weekday hours or 15 weekend hours caring for their sinuses it was considered one household day. The cost to productivity was found to be $10,077 annually per patient living with CRS. This number increased with worsening disease specific QOL scores. Annual productivity costs for other comparable chronic diseases have been found to be less than the productivity cost of CRS. For example, the annual productivity costs of severe asthma, chronic migraine, and diabetes were noted to be $7,260, $5,756, and $3,920 respectively.

Both medical and surgical management play a role in the treatment of CRS. Oral antibiotics are often used in order to attempt to eradicate pathologic bacteria and are most effective when used in a culture directed fashion. As understanding of the pathophysiology of CRS has improved, the role of corticosteroids has increased in attempt to control the inflammatory component of this disease, especially in CRSwNP. Patients often gain a meaningful response when treated with corticosteroids, but this can often be short lived with relapse of symptoms with cessation of the medication. Unfortunately, the side effect profile of prolonged oral corticosteroid use makes long-term treatment with these medications unfavorable.

In the setting of persistent CRS after medical management, endoscopic sinus surgery (ESS) is often considered. Given the chronicity of CRS, surgical intervention does not provide a cure but a tool to help control the disease in the setting of ongoing medical management. The goal of ESS is to identify and widen the natural drainage passages of the paranasal sinuses providing improved ventilation and drainage of the sinuses. Also, removing diseased soft tissue and bone likely decreases the burden of inflammatory infiltrates and infectious microbes. Importantly, the widened opening of the natural drainage passages achieved by ESS allows for the introduction of topical medications in the form of either nasal nebulizers or irrigations for the long-term medical management of the disease process. Many studies have supported the utility of ESS in management of CRS. One prospective multi-institution study randomized patients to surgical intervention or medical management arms. Patients in the ESS arm had significantly greater improvement in the follow up QOL questionnaires and used significantly fewer oral antibiotics and oral steroids.[15] Several systematic reviews have supported the efficacy of ESS and found outcomes to be favorable. A recent review found that of 45 studies that met inclusion criteria, all showed improvement in symptoms or quality of life following surgical intervention.

Given that CRS has been shown to significantly reduce QOL, it has become important to understand both how the disease impacts QOL and how interventions augment this. There are multiple validated questionnaires used to evaluate how symptomatic a patient is due to CRS. One of the most commonly employed scoring systems is the Sinonasal Outcomes Test (SNOT). The SNOT score was initially developed in 1998 and consists of 16 items.[16] The test has been found to be highly

reliable and valid. It has also been shown to correlate well with the SF-36, a measure of general QOL. The original scoring system has undergone multiple revisions with the most recent version consisting of 22 items known as SNOT-22.[17] It has been shown that the minimal clinically important difference (MCID) in SNOT-22 scores is 8.9 points. In order for a patient to detect a difference in symptoms their SNOT-22 score must change by almost 9 points. The SNOT score has been shown to include four specific subdomains including rhinologic, otologic/facial, sleep, and psychologic symptoms.[18,19] This scoring system allows assessment of both rhinologic and non-rhinologic issues.

Given that CRS is a chronic disease, intervention is aimed at controlling symptoms and improving QOL. Many factors have been considered as potential confounders of QOL both before and after ESS. Variables such as polyp status, allergic rhinitis, asthma, gastroesophageal reflux disease, sex, presence of diabetes mellitus, and smoking have all been considered.[20-24] Although age has been considered to some degree, it remains an under-studied factor that could impact the course of CRS as well as outcomes following ESS. It is well established that there are differences in symptomatology, etiology, pathophysiology, and outcomes in pediatric versus adult CRS. There is, however, a dearth of literature evaluating the impact of age among adults on CRS or outcomes following ESS.

One study evaluated the clinical presentation of CRS by age group and noted that patients aged 18-39 years of age were more likely to present with facial pain, have environmental allergies, have anatomic abnormalities, and report improvement in their olfaction following ESS when compared to patients older than 40 years of age.[29] It was also noted that those greater than 60 years of age were more likely to present with

dysosmia, have nasal polyposis, and report improvement in rhinorrhea following surgery when compared to those younger than 60 years of age. It has been reported that the prevalence of CRS among those over 60 years of age was 4.7% making it the sixth most common chronic disease in the elderly. One study attempting to evaluate the course of CRSwNP in elderly patients (≥65 years of age) found that there was a lower recurrence rate after ESS when compared to the younger group.[25] It has also been shown that in a cohort of patients with CRSwNP divided into two groups, age 16-59 and age 60-77, the older group had significantly worse computerized tomography (CT) scores than the younger group.[26] Based on histologic evaluation, there was persistent evidence of impairment of the host innate immunity with age, but that the typical eosinophilic predominance in nasal polyps seems to wane. Based on existing data, there are likely differences in both the presentation of CRS and the outcomes following ESS by age. Objective QOL questions have not yet been used to evaluate the effect of age on outcomes following ESS.

Purpose of the study

To assess how age impacts QOL and patient outcomes following ESS using SNOT-22 questionnaires.

Public health purpose of the study

To aid in guiding management of CRS, a common and costly chronic disease process, with a focus on patient outcomes.

Goal of the study

1) Identify differences in outcomes following ESS stratified by age groups

2) Identify areas for improved patient counseling based on outcomes

CHAPTER II: MANUSCRIPT

Article to be submitted to International Forum of Allergy & Rhinology for publication

Impact of age on outcomes following endoscopic sinus surgery for chronic rhinosinusitis

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Results: The mean age of patients was 48.6 years. Males comprised 55.2% of the patients and most patients were white (87.0%). Polyps were present in 53.9% of patients. Mean SNOT-22 score was 41.0 and was higher in patients younger than 50 years old compared to those of at least 50 years of age. After adjusting for gender, race, polyp status, and number of prior ESS, patients younger than 50 had a higher mean pre-ESS SNOT-22 score (44.0) compared to those of at least 50 years of age (38.9). Among patients younger than 50, SNOT-22 scores declined by 20.7 points at 3 months post-ESS

and 16.1 points at 6 months post-ESS. The rate of change between the dichotomized age groups was not significantly different at 3 and 6 months post-ESS ($p = 0.7952$ and $p = 0.1057$, respectively).

Conclusions: Both age groups showed significant and durable improvement in SNOT-22 scores after ESS. Patients younger than 50 years of age have higher pre-ESS SNOT-22 scores, but converge to have the same SNOT-22 scores at three and six months post-ESS. The rate of change of SNOT-22 scores at three and six months is not different between those younger than 50 years and those of at least 50 years.

Introduction

It is well established that chronic rhinosinusitis (CRS) has a significant effect on quality of life (QOL).[12] When evaluated by the Medical Outcome Study Short-form 36, those affected by CRS were noted to have a significant reduction in measures of general health, bodily pain, vitality, and social functioning when compared to patients without CRS. More recently, it has been noted that CRS leads not only to physical burden but also financial ramifications due to lost productivity.[14] A multitude of studies have supported the utility of endoscopic sinus surgery (ESS) in improving QOL in those with CRS. In one prospective study in which patients were randomized to either ESS or medical management, those who underwent ESS had significantly greater improvement in follow-up QOL questionnaires and required fewer oral antibiotics and steroids.[15] A review of 45 studies evaluating QOL and CRS related symptoms after ESS found that all studies demonstrated improvement after surgical intervention.[27]

Generally, patients with CRS have an overall decrease in QOL; however, patients are affected to differing degrees. Additionally, although patients with CRS generally improve after ESS, some improve more than others. Many factors have been considered as potential confounders of QOL and symptom outcomes both before and after ESS. Variables such as polyp status, allergic rhinitis, asthma, gastroesophageal reflux disease, sex, presence of diabetes mellitus, and smoking have all been considered.[20-24] It is well established that there are differences in symptomatology, etiology, pathophysiology, and outcomes in pediatric versus adult CRS. There is, however, limited data evaluating the impact of age among adults on CRS or outcomes following ESS.

Clinical indications for ESS might differ by age. It has been reported that the prevalence of CRS among those over 60 years of age is 4.7% making it the sixth most common chronic disease in the elderly.[28] One study evaluated the clinical presentation of CRS by age group and noted that patients aged 18-39 years of age were more likely to present with facial pain, have environmental allergies, have anatomic abnormalities, and report improvement in their olfaction following ESS when compared to patients older than 40 years of age.[29] It was also noted that those greater than 60 years of age were more likely to present with dysosmia, have nasal polyposis, and report improvement in rhinorrhea following surgery when compared to those younger than 60 years of age. Another study attempting to evaluate the course of CRSwNP (chronic rhinosinusitis with nasal polyps) in elderly patients (≥65 years of age) found a lower recurrence rate after ESS when compared to the younger group.[25] It has also been shown that in a cohort of patients with CRSwNP divided into two groups, age 16-59 and age 60-77, the older group had significantly worse computerized tomography (CT) scores than the younger group.[26] Based on histologic evaluation, it was noted that there was persistent evidence of impairment of the host innate immunity with age, but the typical eosinophilic predominance in nasal polyps seems to wane.

Existing data indicate that there are differences in both the presentation of CRS and outcomes following ESS by age. Objective QOL questions have not yet been used to evaluate the effect of age on outcomes following ESS. In the current era, in which there is a trend toward individualized treatment of CRS given its varied etiology, it is important to work toward a deeper understanding of why discrepancies exist in outcomes and symptom control to provide improved treatment plans and to better counsel patients on

expected outcomes. The goal of this study is to understand the potential relationship between age, symptom scores, and outcomes following ESS. We hypothesized that those at least 50 years of age will have lower baseline symptom scores than those younger than age 50. Additionally, the change in trajectory of symptom scores overtime will be different between those younger than 50 compared to those 50 or older.

Materials and Methods

The University of Pennsylvania rhinology database was used to identify a case series of 1,252 patients that elected to undergo ESS between the years of 2007 and 2018. Study data were collected and managed using the Research Electronic Data Capture (REDCap) tool hosted at The University of Pennsylvania.[30] This study was approved by the Emory University Institution Review Board (IRB) and deemed exempt by the University of Pennsylvania. Patients that underwent ESS for approach to the orbit or skull base, acute sinusitis, recurrent acute rhinosinusitis, or invasive fungal sinusitis were excluded from analysis. Patients of at least 18 years of age that underwent ESS for CRS with a completed 22-item Sino-Nasal Outcome Test (SNOT-22) questionnaire at a minimum of at least one time point were included in the analysis. The University of Pennsylvania rhinology database was compiled through a retrospective review of both paper and electronic medical records and includes demographic information, diagnosis, baseline Lund-Mackay score, and prospectively collected SNOT-22 scores at baseline, three, six, and twelve months after ESS. The SNOT-22 questionnaire was self-administered in the standard fashion with 22 items graded on a 6-point scale ranging from 0 (no problem) to 5 (problem as bad as can be) with a maximum score of 110 and a minimal clinically important difference (MCID) of 8.9 points.[17] Computed tomography (CT) scoring was

performed using the standardized Lund-Mackay staging system for pre-operative CT scans with total scores ranging from zero to a maximum of 24 points.[31]

Statistical analysis was conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC). The median age of all patients with at least one SNOT-22 score was found to be 50 years. This was thus used to dichotomize age for further comparison of those younger than 50 to those of at least 50 years of age. Descriptive statistics were used to summarize the data with frequency count and percentage reported for categorical variables and mean and standard deviation (SD) reported for continuous variables. Chi square tests and student *t* tests were used for comparisons of categorical and continuous data, respectively. A mixed linear model with an autoregressive error covariance structure was used to evaluate the trend of SNOT-22 score by age group over time and control for gender, race, polyp status, and prior ESS. Time was treated as a categorical variable to allow for nonlinear trends in SNOT-22 scores over time. All confounders being considered were evaluated for their interaction with time. The interaction of the dichotomized age variable and time was retained in the model, as this was a primary question of interest. Tukey's test was used to adjust for multiple comparisons. Alpha was set at 0.05 for all analyses.

In order to evaluate the impact of missing data, the group of patients without either a three or six month SNOT-22 score were compared to the group of patients with either three or six month SNOT-22 scores. Chi square test was used to compare categorical data, while student t test was used to compare continuous data.

Results

Descriptive Analysis

Baseline characteristics

The baseline demographics and clinical characteristics are summarized in Table 1. Of the 1,252 patients that met inclusion criteria for the study, the mean age was 49 years and the median age was 50 years. Of all patients electing to undergo ESS, 55.2% were male with significantly more males in the 50 years and older group ($p = 0.0101$). Patients electing to undergo ESS were predominately white with a significantly higher proportion of white patients in the over 50 group ($p = 0.0049$). Nasal polyps were present in 53.9% of patients with no significant difference between age groups ($p = 0.5390$). The older group of patients had significantly higher number of revision operations ($p = 0.0054$). The mean Lund-Mackay score for all patients electing ESS was 12.3 with no difference between age groups ($p = 0.2048$). The average pre-ESS SNOT-22 score was 41.0 for all patients undergoing ESS with a significantly higher score in those younger than 50 years of age ($p <0.001$).

Analysis of missing data is summarized in Table 2. This analysis revealed some differences between the group of patients without three or six month data compared to the group of patients with either three or six month data. There were more males with SNOT-22 scores at three or six months ($p = 0.0066$). Patients with polyps were more likely to follow up at three or six months ($p = 0.0496$). Patients who had never had prior ESS were less likely to have follow up data, while those with three or more prior ESS were more likely to have follow up data ($p = 0.0223$). Patients with follow up data had a higher baseline Lund-Mackay score (0.0005), but a lower baseline SNOT-22 score ($p = 0.0153$).

Effect of age on SNOT-22

Unadjusted effect of age on SNOT-22 score

Both age groups showed significant improvement at all time points following ESS. The baseline difference noted in SNOT-22 scores persisted at 3 months with patients of at least 50 years of age reporting lower symptom scores ($p = 0.0015$). At 6 months post-ESS there was no difference in symptom scores ($p = 0.2899$), however this difference was seen again at 12 months post-ESS ($p = 0.0374$). The SNOT-22 score at all post-ESS evaluations exceeded the MCID of 9 points in both age groups. Post-ESS symptom scores are summarized in Table 3.

Adjusted effect of age on SNOT-22 score

A model adjusting for effects of potential confounders including gender, race, polyp status, and number of prior ESS on the relationship between age and SNOT-22 scores was evaluated. Adjusting for these potential confounders revealed that the estimated mean pre-ESS SNOT-22 score for those younger than 50 years of age was 44.0 (95% CI 42.2, 45.9) and the estimated mean pre-ESS SNOT-22 score for those 50 or older was 38.9 (95% CI 37.0, 40.7). The scores at three and six months post-ESS were not significantly different ($p = 0.1769$ and 0.8249, respectively). At twelve months post-ESS there is again a significant difference in SNOT-22 scores ($p = 0.0435$). After adjusting for confounders, there was still a significant decline in SNOT-22 scores over time. The rate of decline of SNOT-22 scores between the two age groups was not significantly different at three ($p = 0.7592$) and six months ($p = 0.1057$). However, the rate of change between the two age groups was significant at twelve months ($p = 0.0368$). Patients of at least 50 years of age have lower pre-ESS SNOT-22 scores but the same rate of change of SNOT-

22 scores at three and six months following ESS compared to those younger than 50 years of age. There was a significant difference in the rate of change at twelve months post-ESS with those younger than 50 years having an increase in SNOT-22 scores and those of at least 50 years having a decrease in SNOT-22 scores. Fixed effects of mixed models are summarized in Table 4 and Figure 1.

Discussion

Given the complexity of the etiology of CRS, we adjusted for multiple potential confounders of the relationship between age and SNOT-22 scores including gender, race, polyp status, and number of prior ESS. Adjusting for these variables, patients less than 50 years of age reported higher symptom score prior to surgery. At 3 and 6 months post-ESS visit there was no difference in SNOT-22 scores; this difference reappeared at 12 months post-ESS. However, the results from the 12-month visit should be interpreted with caution. Approximately 2% of patients had follow-up data for the 12-month time point, so these estimates were highly unstable. The increase in SNOT-22 scores for those younger than 50 years seen at this point could represent a tendency to follow up if the patient is still symptomatic. A prior study by Soler and Smith showed the outcomes stabilize at 6 months post-ESS and remain stable until 18 to 20 months.[32] Considering this finding and the low number of scores collected at 12 months in this study, it is likely that the 12 month data is not representative of the overall study population. In order to allow for the inclusion of this 12 month data in the modeling step portion of the analysis despite the high level of missing data points a mixed models approach was used. It should also be noted that the MCID of 8.9 points was surpassed by the 3 month post-ESS visit

and maintained through 12 months post-ESS. On average, patients in both age groups undergoing ESS achieved a meaningful and durable improvement in symptom scores.

There was a significant decline in symptom scores in both age groups over time. The decline was similar in magnitude and slope at three and six months while adjusting for the previously mentioned confounders between those younger than 50 years of age and those of at least 50 years of age. Of note, 55.2% of all patients electing ESS were male with a significantly higher proportion of males in the 50 years and older group. Prior research by Lal[33,34] showed that men report significantly lower SNOT-22 scores when compared to women with a decline in SNOT-22 scores with age for both sexes. Sex was included in the model in order to adjust for this effect.

Recent research has postulated that the drop in symptom score with age could be due to a decline in disease severity with age noting a decline in Lund-Mackay CT scores for men.[34] Our study found no difference in Lund-Mackay score between the two age groups while adjusting for sex. The two studies used different age groups for analysis so direct comparison is not possible. A different age cut off than the one we used might show declining CT scores in our data as well. By the nature of the design of this study an equivalent number of patients in the younger and older age groups elected to proceed with ESS. This implies that disease severity was judged to be similar between the groups. Given no difference in Lund-Mackay score between age groups, but significantly different symptom scores, it is possible that rhinologists rely more heavily on evaluation of the disease severity on CT scan than the symptom scores when discussing the option of surgical intervention with patients despite the lack of correlation between CT scores and symptom scores.[35] Additionally, symptoms of allergic rhinitis have been reported to

decline with age.[36] Details on allergy status were not available and were thus not considered in the analysis. It is possible that allergic status and symptoms could account for some of the difference seen between the two age groups.

Limitations

This is a retrospective study and relies on data collected in the medical records leading to high levels of missing data. Analysis of missing data showed that there were some differences between those who followed up at three or six months compared to those who did not. This might result in bias of the observed associations. For example, this could lead to a selection bias with those with worse disease severity or persistent symptoms being more likely to follow up.

Both SNOT-22 scores and Lund-Mackay CT scores were obtained prospectively. Only those ultimately electing to undergo ESS were included for evaluation. There is no data available on those who were candidates, but elected to forgo ESS. Another important consideration is the lack of subdomain data for SNOT-22 scores. This was not available for analysis but could contain interesting information regarding differences between age groups. Patients 60 years or older present more commonly with dysosmia and report improvement in rhinorrhea following surgery; patients age 18-39 present most commonly with facial pain and rhinorrhea, but report more improvement in olfaction.[29]

There are other potentially meaningful confounders that were not considered in this report that could augment outcomes following ESS. Prior work by Cho[26] noted in patients with CRSwNP, those of at least 60 years of age had higher CT scores, but lower levels of eosinophilia. This raises the possibility that changes occurring on a cellular level could impact the relationship of age with outcomes scores. Unfortunately, data regarding

cigarette smoking status, psychological symptoms, and the need for or adherence to medical management in the postoperative period were not available. It is possible that there are differences in these or other yet unrecognized confounders that could be accounting for some of the differences between age groups identified in this analysis. Another interesting area for consideration is the role of generational or societal norms that occur with age and how this affects subjective reporting of symptom severity. Older generations have had more life experience and could be more likely to report lower symptom scores despite having similar disease severity. This is a very complex question that warrants further investigation.

Conclusion

Both patients younger than 50 years and those of at least 50 years showed significant and durable improvement in SNOT-22 scores after ESS. Patients younger than 50 years of age have higher pre-ESS SNOT-22 scores, but converge to have the same SNOT-22 scores at three and six months post-ESS. The rate of change of SNOT-22 scores at three and six months is not different between those younger than 50 years and those of at least 50 years.

Table 1: Baseline demographics and summary statistics.

	All patients	<50 years	≥50 years	p-value
Characteristics	(n = 1,252)	(n = 618)	(n = 634)	
Age (years), mean (SD)	48.6 (14.7)	36.3 (8.7)	60.6 (7.8)	<0.0001
Gender (male), n (%)	688 (55.2)	317 (51.5)	371 (58.8)	0.0101
Race (white), n (%)	1,115 (87.0)	536 (86.3)	579 (91.9)	0.0049
Polyps n (%)	574 (53.9)	292 (54.8)	282 (52.9)	0.5390
Revision ESS n (%)				
0	451 (36.2)	250 (40.7)	201 (31.9)	
1-2	556 (44.7)	258 (42.0)	298 (23.9)	0.0054
≥3	238 (19.1)	107 (17.4)	131 (20.8)	
Lund-Mackay Score mean (SD)	12.3 (6.2)	12.6 (6.4)	12.1 (5.9)	0.2048
SNOT-22 Score mean (SD)	41.0 (22.5)	43.7 (22.8)	38.3 (22.0)	<0.0001

SD = standard deviation; ESS = endoscopic sinus surgery; SNOT-22 = 22-item Sino-Nasal Outcome Test.

Table 2: Comparison of data between patients without a SNOT-22 score at 3 or 6 months post-ESS to those with a score at either 3 or 6 months post-ESS

	Data without either 3 or 6 month SNOT-22 score n = 1518	Data with either 3 or 6 month SNOT-22 score n = 341	Chi Square p-value
Baseline data (Categorical)	n(%)	n(%)	
Age			
<50	765(50.4)	155(45.5)	
≥50	753(49.6)	186(54.6)	0.0992
Gender			
Male	785(52.0)	205(60.1)	
Female	725(48.0)	136(39.9)	*0.0066
Race			
White	1328(88.7)	309(90.6)	
Other	170(11.4)	32(9.4)	0.2951
Polyp Status			
No	566(46.2)	105(39.6)	
Yes	658(53.8)	160(60.4)	*0.0496
Revision ESS			
0	545(37.3)	107(31.5)	
1-2	667(45.6)	155(45.6)	
≥3	78(17.2)	78(22.9)	*0.0223
Baseline data (Continuous)	Mean (SD)	Mean (SD)	t-test p-value
Lund MacKay Score	12.1 (6.2)	13.7 (6.2)	*0.0005
Baseline SNOT Score	41.9 (23.0)	38.4 (21.2)	*0.0153

* Highlights significant difference between groups
SNOT-22 = 22-item Sino-Nasal Outcome Test; SD = standard deviation; ESS = endoscopic sinus surgery

Table 3: Unadjusted effect of age dichotomized by age 50 on SNOT-22 scores over time

	All patients	<50 years	≥50 years	p-value
	mean (SD)	mean (SD)	mean (SD)	
Baseline (n = 1,246)	41.0 (22.5)	43.7 (22.8)	38.3 (22.0)	<0.0001
3-months post-ESS (n = 290)	20.0 (18.2)	23.8 (20.3)	17.0 (15.7)	0.0015
6-months post-ESS (n = 241)	21.0 (18.4)	22.5 (20.9)	19.9 (16.5)	0.2899
12-months post-ESS (n = 25)	20.4 (17.1)	33.8 (21.3)	14.2 (10.4)	0.0374

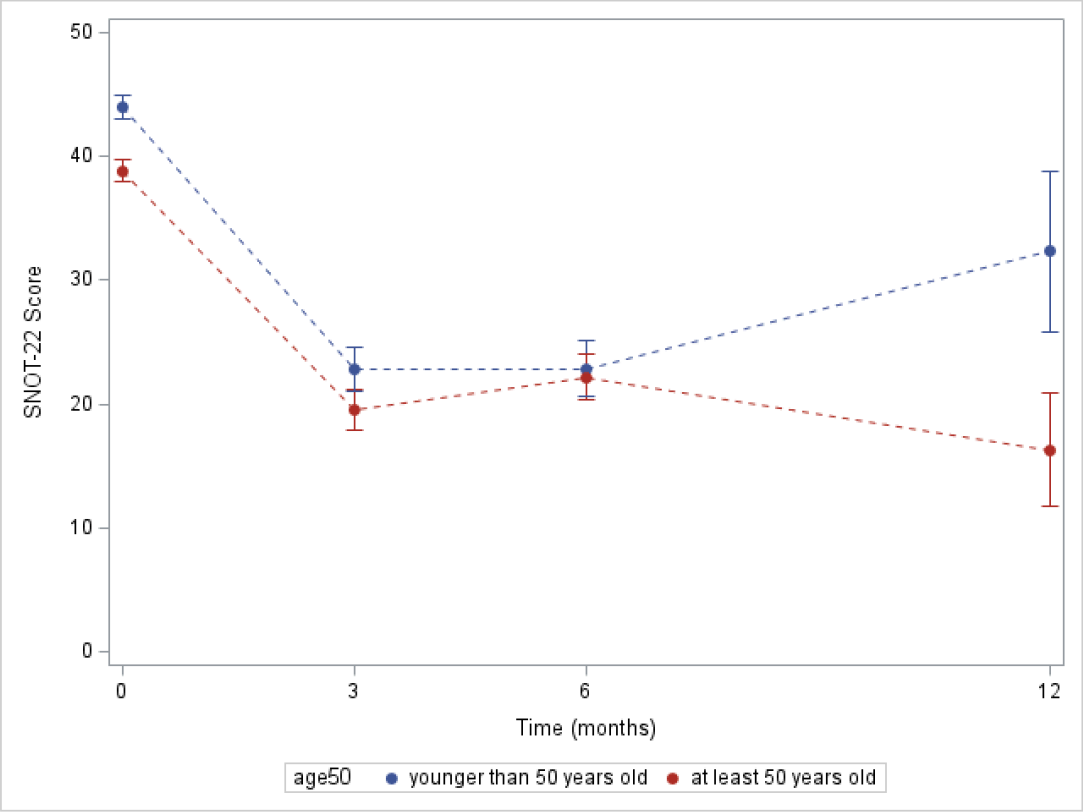
SNOT-22 = 22-item Sino-Nasal Outcome Test; SD = standard deviation; ESS = endoscopic sinus surgery

Table 4: Adjusted effect of age dichotomized by age 50 on SNOT-22 scores over time

	<50 years	≥50 years	p-value
	mean (95% CI)	mean (95% CI)	
Baseline SNOT-22 (n = 1,246)	44.0 (42.2, 45.9)	38.9 (37.0, 40.7)	<0.0001
3-months post-ESS SNOT-22 (n = 290)	22.8 (19.3, 26.4)	19.5 (16.4, 22.7)	0.1769
6-months post-ESS SNOT-22 (n = 241)	22.9 (18.4, 27.4)	22.2 (18.5, 25.9)	0.8249
12-months post-ESS SNOT-22 (n = 25)	32.4 (19.6, 45.1)	16.3 (7.3, 25.3)	0.0435

SNOT-22 = 22-item Sino-Nasal Outcome Test; SD = standard deviation; ESS = endoscopic sinus surgery

Figure 1: Adjusted effect of age dichotomized at 50 years on SNOT-22 scores over time



CHAPTER III: RESULTS

Descriptive Analysis

Baseline characteristics

The baseline demographics and clinical characteristics are summarized in Table 1. Of the 1,252 patients that met inclusion criteria for the study, the mean age was 49 years and the median age was 50 years. Of all patients electing to undergo ESS, 55.2% were male with significantly more males in the 50 years and older group ($p = 0.0101$). Patients electing to undergo ESS were predominately white with a significantly higher proportion of white patients in the over 50 group ($p = 0.0049$). Nasal polyps were present in 53.9% of patients with no significant difference between age groups ($p = 0.5390$). The older group of patients had significantly higher number of revision operations ($p = 0.0054$). The mean Lund-Mackay score for all patients electing ESS was 12.3 with no difference between age groups ($p = 0.2048$). The average pre-ESS SNOT-22 score was 41.0 for all patients undergoing ESS with a significantly higher score in those younger than 50 years of age ($p <0.001$).

Analysis of missing data is summarized in Table 2. This analysis revealed some differences between the group of patients without three or six month data compared to the group of patients with either three or six month data. There were noted to be more males with SNOT-22 scores at three or six months ($p = 0.0066$). Patients with polyps were more likely to follow up at three or six months ($p = 0.0496$). Patients who had never had prior ESS were less likely to have follow up data, while those with three or more prior ESS were more like to have follow up data

(p = 0.0223). Patients with follow up data had a higher baseline Lund-Mackay score (0.0005), but a lower baseline SNOT-22 score (p = 0.0153).

Effect of age on SNOT-22 score

Unadjusted effect of age on SNOT-22 score

Both age groups showed significant improvement at all time points following ESS. The baseline difference noted in SNOT-22 scores persisted at 3 months with patients of at least 50 years of age reporting lower symptom scores (p = 0.0015). At 6 months post-ESS there was no difference in symptom scores (p = 0.2899), however this difference was seen again at 12 months post-ESS (p = 0.0374). The SNOT-22 score at all post-ESS evaluations exceeded the MCID of 8.9 points in both age groups. Unadjusted post-ESS symptom scores are summarized in Table 3.

Unconditional means model

The unconditional means model determined that there was sufficient systemic variation in the outcome of interest, SNOT-22 scores, to warrant further exploration. Evaluation of the random effects of the unconditional growth model revealed that there was remaining residual variability both within (p <0.0001) and between persons (p <0.0001). This implies that further evaluation of both time-varying and time-invariant predictors could identify relationships between these predictors and SNOT-22 scores. The intraclass correlation coefficient showed that 38.8% of total variation in the SNOT-22 scores was attributable to differences between patients, while the remaining 62.2% of the total variation was due to differences within patients.

Unconditional growth model

Next, the unconditional growth model, with only the temporal predictor of time, was explored. This revealed that the estimated pre-ESS mean SNOT-22 score of all patients included in the study was 39.9 (95% CI 38.7, 41.2) and that among all patients this score decreased by 3.4 points per month ($p < 0.0001$). Review of the random effects of the unconditional growth model revealed that accounting for time, the level 1 residual variance showed remaining within person variability. The level 2 residual variance of the pre-ESS SNOT-22 score ($p < 0.0001$) and the monthly rate of change of SNOT-22 score ($p = 0.0002$) identified that there was persistent heterogeneity and variability implying the need for additional predictors in the model. The correlation between true rate of change and pre-ESS SNOT-22 score was strong at 0.69. It was noted that 34.3% of within-person variation in SNOT-22 score was associated with linear time. This implies that the addition of further time-varying predictors could be useful, however no other time-varying predictors are available in this dataset. Using the pseudo R^2 statistic it was determined that 12.4% of total variation in SNOT-22 score is associated with linear time, again reaffirming the need for the addition of predictors to the model. Both the assumptions of independence and homoscedasticity were violated and thus supported the use of the mixed models approach to data modeling.

Effect of age and time on SNOT-22 scores

Given the preceding tests of hypothesis revealed statistically significant variability in both true initial status and true rate of change, level two predictors were added to the model to attempt to account for unexplained heterogeneity. The addition of the

dichotomous age variable to the model revealed that the estimated mean pre-ESS SNOT-22 score for those younger than 50 years of age was 42.8 (95% CI 41.0, 44.6), while the estimated mean SNOT-22 score for those of at least 50 years of age was 37.1 (95% CI 32.9, 41.4). The difference in pre-ESS SNOT-22 scores between those less than 50 years of age compared to those 50 years of age or older was statistically significant in the uncontrolled effects of age model ($p < 0.0001$). Additionally, it was noted that the SNOT-22 score decreases at a statistically significant rate of 3.6 points per month for those younger than 50 ($p < 0.0001$) and it decreases by 3.2 points for those 50 or older. The rate of change of SNOT-22 scores between the two age groups was not significantly different in this unadjusted model ($p = 0.2050$). In sum, the unadjusted effect of age model concludes that patients of at least 50 years of age have lower pre-ESS SNOT-22 scores, but the same monthly rate of change of SNOT-22 scores over time compared to those younger than 50 years of age.

Review of the level 2 random effects of this model revealed that there is persistent residual variance of the pre-ESS SNOT-22 score after controlling for the effect of age. This dichotomous age variable accounts for 3.1% of variability in the pre-ESS SNOT-22 score. Additionally, there is persistent variation in the monthly rate of change of SNOT-22 score after accounting for dichotomized age. Given this persistent heterogeneity additional level 2 predictors were incorporated into the model. A delta deviance test comparing the model with age to the model without age was performed and showed that the model with the dichotomized age variable had an improved fit ($p = 0.0001$). The dichotomized age variable was therefore kept in the model.

Adjusted effect of age on SNOT-22 score

A model adjusting for effects of potential confounders including gender, race, polyp status, and number of prior ESS on the relationship between age and SNOT-22 scores was evaluated. Adjusting for these potential confounders revealed that the estimated mean pre-ESS SNOT-22 score for those younger than 50 years of age was 44.0 (95% CI 42.2, 45.9) and the estimated mean pre-ESS SNOT-22 score for those 50 or older was 38.9 (95% CI 37.0, 40.7). The scores at three and six months post-ESS were not significantly different ($p = 0.1769$ and 0.8249, respectively). At twelve months post-ESS there is again a significant difference in SNOT-22 scores ($p = 0.0435$). After adjusting for confounders, there was still a significant decline in SNOT-22 scores over time. The rate of decline of SNOT-22 scores between the two age groups was not significantly different at three ($p = 0.7592$) and six months ($p = 0.1057$). However, the rate of change between the two age groups was significant at twelve months ($p = 0.0368$). Patients of at least 50 years of age have lower pre-ESS SNOT-22 scores but the same rate of change of SNOT-22 scores at three and six months following ESS compared to those younger than 50 years of age. There was a significant difference in the rate of change at twelve months post-ESS with those younger than 50 years having an increase in SNOT-22 scores and those of at least 50 years having a decrease in SNOT-22 scores. Fixed effects of mixed models are summarized in Table 4 and Figure 1.

CHAPTER IV: DISCUSSION

Given the complexity of the etiology of CRS, this study adjusted for multiple potential confounders of the relationship between age and SNOT-22 scores including gender, race, polyp status, and number of prior ESS. Adjusting for these variables, patients less than 50 years of age reported higher symptom score prior to surgery. At 3 and 6 months post-ESS visit there was no difference in SNOT-22 scores. However, this difference reappeared at 12 months post-ESS. However, the results from the 12-month visit should be interpreted with caution. Approximately 2% of patients had follow-up data for the 12-month time point, so these estimates were highly unstable. The increase in SNOT-22 scores for those younger than 50 years seen at this point could represent a tendency to follow up if the patient is still symptomatic. A prior study by Soler and Smith showed the outcomes stabilize at 6 months post-ESS and remain stable until 18 to 20 months.[32] With this study in mind and the low number of scores collected at 12 months in this study, it is most reasonable to assume the 12 month data is not representative of the study population. In order to allow for the inclusion of this 12 month data in the modeling step portion of the analysis despite the high level of missing data points a mixed models approach was used. It should also be noted that the MCID of 8.9 points was surpassed by the 3 month post-ESS visit and maintained through 12 months post-ESS. On average, patients in both age groups undergoing ESS achieved a meaningful and durable improvement in symptom scores.

There was noted to be a significant decline in symptom scores in both age groups overtime. The decline was similar in magnitude and slope while adjusting for

the previously mentioned confounders between those younger than 50 years of age and those of at least 50 years of age. Of note, 55.2% of all patients electing ESS were male with a significantly higher proportion of males in the 50 years and older group. Prior research by Lal[33,34] showed that men report significantly lower SNOT-22 scores when compared to women with a decline in SNOT-22 scores with age for both sexes. Sex was included in the model in order to eliminate any potential effect it might have on outcomes.

Recent research has postulated that the drop in symptom score with age could be due to a decline in disease severity with age noting a decline in Lund-Mackay CT scores for men.[34] This study found no difference in Lund-Mackay score between the two age groups while adjusting for sex. However, the two studies used different age groups for analysis so direct comparison is not possible. It is possible that analyzing a higher age cut off would show declining CT scores in this dataset as well. By the nature of the design of this study an equivalent number of patients in the younger and older age groups elected to proceed with ESS. This implies that disease severity was judged to be similar between the groups. Given no difference in Lund-Mackay score between age groups, but significantly different symptom scores, it is possible that rhinologists rely more heavily on evaluation of the disease severity on CT scan than the symptom scores when discussing the option of surgical intervention with patients despite the lack of correlation between CT scores and symptom scores.[35] Additionally, symptoms of allergic rhinitis have been reported to decline with age.[36] Details on allergy status were not available and were thus not considered in the

analysis. It is possible that allergic status and symptoms could account for some of the difference seen between the two age groups.

CRS occurs in all age groups with true prevalence difficult to determine given the lack of standardization of how data is collected. The prevalence of CRS in those over 60 years of age has been reported to be 4.7% making it the sixth most common chronic disease of the elderly. It was shown that there is a lower revision rate of ESS in those ≥65 years of age when compared to a younger group.[25] In another cohort of patients with CRSwNP, those 60-77 had higher CT scores than those aged 16-59.[26] It is interesting to consider when comparing these two studies that the older age group had worse CT scores, but required fewer revision ESS. This indicates that there might be differences in how older patients respond to sinus surgery. It has also been determined that those older than 60 have lower predominance of eosinophils. Typically, this lack of eosinophilia renders a patient less likely to respond to the most common medical management after ESS, corticosteroids, meaning those over 60 would theoretically be more difficult to manage medically. It is possible that this could represent a different variant of CRS in those over 60. Alternatively, it could be that there is simply less time to have revision ESS.

Limitations

This is a retrospective study and relies on data gleaned from the medical records leading to high levels of missing data. Analysis of missing data showed that there were some differences between those who followed up at three or six months compared to those who did not. It is important to question the impact that those who not represented in the analysis could have had on the outcome. This could lead to a

selection bias with those with worse disease severity or persistent symptoms being more likely to follow up. It should be noted that both SNOT-22 scores and Lund-Mackay CT scores were obtained prospectively. Only those ultimately electing to undergo ESS were included for evaluation. There is no data available on those who were candidates, but elected to forgo ESS. Another important consideration is the lack of subdomain data for SNOT-22 scores. This was unfortunately not available for analysis, but could contain interesting information regarding differences between age groups. It has previously been shown that patients 60 years or older present more commonly with dysosmia and report improvement in rhinorrhea following surgery, while those age 18-39 present most commonly with facial pain and rhinorrhea, but report more improvement in oflaction.[29]

There are other potentially meaningful confounders that were not considered in this report that could augment outcomes following ESS. Prior work by Cho[26] noted in patients with CRSwNP those of at least 60 years of age had higher CT scores, but lower levels of eosinophilia. This raises the possibility that changes occurring on a cellular level could impact the relationship of age with outcomes scores. Unfortunately, data regarding cigarette smoking status, psychological symptoms, the need for or adherence to medical management in the postoperative period, were not available. It is possible that there are differences in these or other yet unrecognized confounders that could be accounting for some of the differences between age groups identified in this analysis. Another interesting area for consideration is the role of generational or societal norms that occur with age. It should be considered that older generations have experienced more in their lifetimes and could be more likely to

report lower symptom scores despite having similar disease severity. This is a very complex question that warrants further investigation.

Public Health Implications

CRS leads to dramatic decrease in QOL and personal financial repercussions due to a decline in productivity. Additionally, the cost of this disease process to society is staggering with the estimated annual economic burden to the United States approaching 22 billion dollars annually.[13] It is important to continue to gain a deeper understanding of this disease process in order to better understand which patients will do well following ESS and how best to counsel these patients. Patients undergoing surgical intervention take a significant risk and should be educated properly on their projected course following ESS. Continuing to work toward this depth of understanding will ultimately lead to improved treatment plans and improved communication with patients.

Future Directions

It will be important to collect data regarding the question of age and outcomes following ESS in a prospective fashion. This would allow for collection of data in a more methodical and meaningful way. Prospective data collection should include evaluation of subdomain level data of SNOT-22 scores to evaluate for the potential variations in both rhinologic and non-rhinologic symptoms reported by age. This would also allow for evaluation of the role of other important potential confounders such as psychiatric disease, allergic rhinitis, and sleep disorders that impact SNOT-22 total scores. Additionally, an assessment of a variety of different age groups and smaller age ranges could lead to more specific information regarding the role of age.

This would require more patients in order to have enough data for meaningful analysis.

It will be important to continue to move toward a deeper understanding of the pathophysiology of this complex process. Understanding which patients are most at risk and which are most likely to fail traditional treatment will lead to a dramatic improvement in patient care for this costly and debilitating disease.

REFERENCES

1. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical practice guideline (update): Adult Sinusitis Executive Summary. *Otolaryngol Head Neck Surg.* 2015;152(4):598-609.
2. Lee S, Lane AP. Chronic rhinosinusitis as a multifactorial inflammatory disorder. *Curr Infect Dis Rep.* 2011;13(2):159-168.
3. Drake-Lee AB, McLaughlan P. Clinical symptoms, free histamine and IgE in patients with nasal polyposis. *Int Arch Allergy Appl Immunol.* 1982;69(3):268-271.
4. Pawankar R, Nonaka M. Inflammatory mechanisms and remodeling in chronic rhinosinusitis and nasal polyps. *Curr Allergy Asthma Rep.* 2007;7(3):202-208.
5. Ou J, Wang J, Xu Y, et al. Staphylococcus aureus superantigens are associated with chronic rhinosinusitis with nasal polyps: a meta-analysis. *Eur Arch Otorhinolaryngol.* 2014;271(10):2729-2736.
6. Ramakrishnan Y, Shields RC, Elbadawey MR, Wilson JA. Biofilms in chronic rhinosinusitis: what is new and where next? *J Laryngol Otol.* 2015;129(8):744-751.
7. Rudmik L. Chronic rhinosinusitis: an under-researched epidemic. *J Otolaryngol Head Neck Surg.* 2015;44:11.
8. Chen Y, Dales R, Lin M. The epidemiology of chronic rhinosinusitis in Canadians. *Laryngoscope.* 2003;113(7):1199-1205.
9. Blackwell DL, Lucas JW, Clarke TC. Summary health statistics for U.S. adults: national health interview survey, 2012. *Vital Health Stat 10.* 2014(260):1-161.
10. Lee LN, Bhattacharyya N. Regional and specialty variations in the treatment of chronic rhinosinusitis. *Laryngoscope.* 2011;121(5):1092-1097.
11. Soler ZM, Mace JC, Litvack JR, Smith TL. Chronic rhinosinusitis, race, and ethnicity. *Am J Rhinol Allergy.* 2012;26(2):110-116.
12. Gliklich RE, Metson R. The health impact of chronic sinusitis in patients seeking otolaryngologic care. *Otolaryngol Head Neck Surg.* 1995;113(1):104-109.
13. Smith KA, Orlandi RR, Rudmik L. Cost of adult chronic rhinosinusitis: A systematic review. *Laryngoscope.* 2015;125(7):1547-1556.
14. Rudmik L, Smith TL, Schlosser RJ, Hwang PH, Mace JC, Soler ZM. Productivity costs in patients with refractory chronic rhinosinusitis. *Laryngoscope.* 2014;124(9):2007-2012.
15. Smith TL, Kern RC, Palmer JN, et al. Medical therapy vs surgery for chronic rhinosinusitis: a prospective, multi-institutional study. *Int Forum Allergy Rhinol.* 2011;1(4):235-241.
16. Anderson ER, Murphy MP, Weymuller EA, Jr. Clinimetric evaluation of the Sinonasal Outcome Test-16. Student Research Award 1998. *Otolaryngol Head Neck Surg.* 1999;121(6):702-707.
17. Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. *Clin Otolaryngol.* 2009;34(5):447-454.

18. Nanayakkara JP, Igwe C, Roberts D, Hopkins C. The impact of mental health on chronic rhinosinusitis symptom scores. *Eur Arch Otorhinolaryngol.* 2013;270(4):1361-1364.
19. Pynnonen MA, Kim HM, Terrell JE. Validation of the Sino-Nasal Outcome Test 20 (SNOT-20) domains in nonsurgical patients. *Am J Rhinol Allergy.* 2009;23(1):40-45.
20. DelGaudio JM. Direct nasopharyngeal reflux of gastric acid is a contributing factor in refractory chronic rhinosinusitis. *Laryngoscope.* 2005;115(6):946-957.
21. Smith TL, Mendolia-Loffredo S, Loehrl TA, Sparapani R, Laud PW, Nattinger AB. Predictive factors and outcomes in endoscopic sinus surgery for chronic rhinosinusitis. *Laryngoscope.* 2005;115(12):2199-2205.
22. Houser SM, Keen KJ. The role of allergy and smoking in chronic rhinosinusitis and polyposis. *Laryngoscope.* 2008;118(9):1521-1527.
23. Pearlman AN, Chandra RK, Chang D, et al. Relationships between severity of chronic rhinosinusitis and nasal polyposis, asthma, and atopy. *Am J Rhinol Allergy.* 2009;23(2):145-148.
24. Zhang Z, Adappa ND, Lautenbach E, et al. The effect of diabetes mellitus on chronic rhinosinusitis and sinus surgery outcome. *Int Forum Allergy Rhinol.* 2014;4(4):315-320.
25. Brescia G, Barion U, Pedruzzi B, et al. Sinonasal polyposis in the elderly. *Am J Rhinol Allergy.* 2016;30(5):153-156.
26. Cho SH, Hong SJ, Han B, et al. Age-related differences in the pathogenesis of chronic rhinosinusitis. *J Allergy Clin Immunol.* 2012;129(3):858-860 e852.
27. Smith TL, Batra PS, Seiden AM, Hannley M. Evidence supporting endoscopic sinus surgery in the management of adult chronic rhinosinusitis: a systematic review. *Am J Rhinol.* 2005;19(6):537-543.
28. Marioni G, Zanotti C, Brescia G. Chronic rhinosinusitis with nasal polyps in the elderly: Assessing current evidence. *Allergy Asthma Proc.* 2018;39(1):9-13.
29. Busaba NY. The impact of a patient's age on the clinical presentation of inflammatory paranasal sinus disease. *Am J Otolaryngol.* 2013;34(5):449-453.
30. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009;42(2):377-381.
31. Lund VJ, Kennedy DW. Staging for rhinosinusitis. *Otolaryngol Head Neck Surg.* 1997;117(3 Pt 2):S35-40.
32. Soler ZM, Smith TL. Quality-of-life outcomes after endoscopic sinus surgery: how long is long enough? *Otolaryngol Head Neck Surg.* 2010;143(5):621-625.
33. Lal D, Golisch KB, Elwell ZA, Divekar RD, Rank MA, Chang YH. Gender-specific analysis of outcomes from endoscopic sinus surgery for chronic rhinosinusitis. *Int Forum Allergy Rhinol.* 2016;6(9):896-905.

34. Lal D, Rounds AB, Divekar R. Gender-specific differences in chronic rhinosinusitis patients electing endoscopic sinus surgery. *Int Forum Allergy Rhinol.* 2016;6(3):278-286.
35. Bhattacharyya N. Radiographic stage fails to predict symptom outcomes after endoscopic sinus surgery for chronic rhinosinusitis. *Laryngoscope.* 2006;116(1):18-22.
36. Di Lorenzo G, Leto-Barone MS, La Piana S, Ditta V, Di Fede G, Rini GB. Clinical course of rhinitis and changes in vivo and in vitro of allergic parameters in elderly patients: a long-term follow-up study. *Clin Exp Med.* 2013;13(1):67-73.