

Impact of medically recalcitrant chronic rhinosinusitis on incidence of asthma

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Background: The long-term impact of chronic rhinosinusitis (CRS) with or without allergic rhinitis (AR) on asthma is poorly documented. This study analyzed potential associations of ongoing CRS and AR on asthma.

Methods: Using the MarketScanTM claims database, patients with CRS and endoscopic sinus surgery (ESS) in 2010 were identified. The date of first sinusitis was determined for all. Patients with asthma at time of first sinusitis diagnosis were excluded. The remaining patients were grouped based on duration of sinusitis, from first diagnosis to surgery—group 1: 1 to <2 years (n = 181); group 2: 2 to <3 years (n = 195); group 3: 3 to <4 years (n = 292); and group 4: 4 to <5 years (n = 536). Yearly incidence and prevalence of newly diagnosed asthmatics was analyzed for all groups. A secondary analysis evaluated the association between AR and asthma.

Results: Preoperatively, yearly incidence of patients with new asthma diagnoses averaged 4.48% (95% confidence interval [CI], 3.93% to 5.11%) and was significantly greater for patients with AR (5.93%; 95% CI, 4.56% to 7.66%) vs non-

AR (4.15%; 95% CI, 3.56% to 4.82%); $p = 0.03$. Postoperatively, yearly incidence of asthma was 0.42% (95% CI, 0.18% to 0.88%). No patient had asthma at time of first diagnosis; however, by time of surgery, 9.4%, 12.8%, 18.2%, and 22.40% of patients had been diagnosed with asthma, in groups 1 through 4, respectively.

Conclusion: AR was a significant risk factor for asthma in patients with CRS. Medically recalcitrant CRS was associated with high incidence rates of asthma, which declined post-operatively. Patients operated earlier in the disease continuum were therefore at decreased risk of developing asthma. © 2015 ARS-AAOA, LLC.

Key Words: rhinosinusitis; allergic rhinitis; asthma; incidence; database

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The association between allergic rhinitis (AR) and asthma has been previously recognized, and prior studies have suggested that up to 40% of people with AR may develop asthma in the general population.^{1,2}

Although AR and asthma may therefore be associated, the association of chronic rhinosinusitis (CRS) with AR and asthma is less well studied. Recent observational studies

have reported rates of comorbidities in patients with CRS at various stages of disease, but overall, the natural history of CRS and expected progressions from CRS to associated comorbidities is largely unknown. These studies suggested that early surgical management of CRS could reduce long-term healthcare burden and may be associated with lower incidence of asthma.³⁻⁵

This study was therefore designed to evaluate 2 separate hypotheses: (1) patients with ongoing medically recalcitrant CRS are at increased risk of being diagnosed for asthma vs patients surgically treated for CRS; and (2) AR increases risk for asthma in patients with CRS. Our study was based on the following assumptions: (1) patients requiring continuous care for CRS, leading eventually to surgery, have ongoing, medically recalcitrant CRS until surgery;⁶ and (2) surgery is more effective than medical management in these patients and for most patients, will allow significant reduction of CRS symptoms, at least for the first few postoperative years.⁷

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A significant challenge with designing this study was the need for large patient cohorts with significant periods of available medical history both preoperatively, during the ongoing, medically recalcitrant CRS state, and postoperatively. To address this need, the MarketScanTM Commercial Claims and Encounter database was selected. This database includes all medical (primary and specialized care) inpatient and outpatient encounters, as well as complete prescription history for all patients, and has been utilized extensively for paranasal sinus-related studies.^{8,9} In recent years, this database has included more than 30 million distinct lives per year. More specifically, this database captures each medical visit, including operating room and emergency room visit, with all diagnoses, tests, and procedures performed during that visit. Physician type and payment information are also captured. Although prescriptions are not linked to specific visits, detailed prescription details in terms of drug name, date, category, and dosage are available for all patients. More importantly, patients—including their complete demographic information—are tracked longitudinally, such that complete patient medical histories may be in the database for multiple continuous years.

Patients and methods

This study was a retrospective analysis of a large administrative database containing medical and drug claims for reimbursement purposes (also known as claims-based analysis) with no identification of individual patients, and therefore was exempt from the need to obtain Institutional Review Board (IRB) approval.

Cohort identification

The general patient cohort was identified as described.⁵ Briefly, all patients in the cohort had a primary sinus surgery for CRS in 2010 (no prior sinus surgery before that “index surgery”) and continuous enrollment in the database from January 1, 2004, to December 31, 2012. The date of each patient’s first sinusitis or polyposis diagnosis (“first diagnosis”) was identified and the time interval from first diagnosis to index surgery was calculated for all. Patients had a period of at least 12 months prior to their first diagnosis, during which time they had no sinus/polyp diagnoses or procedures (“washout period”). All patients in the cohort were treated medically following their first diagnosis. Medical treatment was defined as a prescription for medication belonging to the antibiotics and/or corticosteroids drug categories, within 14 days of a sinus/polyp diagnosis. Patients with diagnoses of asthma (International Classification of Diseases, 9th edition [ICD-9] codes 493.XX and V17.5) prior to their first diagnosis were eliminated from the study. Patients were further defined based on whether or not they had AR (ICD-9 code 477.8 and 477.9) at time of first diagnosis.

The following groups of patients were thus formed, based on time from first diagnosis to index surgery—group 1: 1

up to <2 years; group 2: 2 up to <3 years; group 3: 3 up to <4 years; and group 4: 4 up to <5 years.

Additional comorbid conditions

All patients’ outpatient records were queried for primary or secondary diagnoses of the following additional comorbidities: nasal polyposis (ICD-9 codes 471.X), aspirin sensitivity (ICD-9 codes 995.0, 995.2, 995.20, 995.27, 995.29, 995.3, V14.6, V14.8), diabetes (ICD-9 codes 250.XX), and depression (ICD-9 code 311 and 300.4). Patients were also diagnosed as having Samter’s triad if they had concurrent diagnoses of aspirin sensitivity, polyposis, and asthma.

Identification of new asthma diagnosis after first diagnosis

From the time of first diagnosis up to 2 years postoperatively, the outpatient and inpatient medical history of all patients was analyzed for new diagnoses of asthma (primary or secondary). When patients presented with new diagnoses of asthma, the timing of these diagnoses was defined as: (1) number of years between first diagnosis and new asthma diagnosis; (2) occurrence of new asthma diagnosis pre- vs post-index surgery; (3) if postsurgery: number of years after index surgery. The overall incidence of new asthma cases and overall prevalence of patients having received an asthma diagnosis was defined for all groups for patients with AR vs patients without AR.

Statistical analysis

For each patient group, descriptive statistics and analyses (mean, standard errors of the means, confidence intervals; $\alpha = 0.05$) were determined for continuous values such as age. Proportions of patients presenting with asthma diagnoses in the AR and non-AR groups and before and after index surgery were calculated and confidence intervals for proportions were derived using the Wald method. Proportions were compared using Fisher’s exact test for unpaired groups. The time to asthma was further analyzed for patients in group 4 using a Kaplan-Meier survival curve (all data beyond 6 years [after surgery] being censored for the purpose of the analysis). Confidence bands around the survival curve are presented and log-rank tests were performed to compare preoperative incidence of asthma diagnoses in group 4 patients with and without AR. Proportional hazard analyses were further conducted in group 4, comparing patients with and without AR, to further determine impact of AR and also whether age or gender impacted risk of being diagnosed with asthma.

Results

Table 1 shows demographic and key comorbid conditions for patients in each group at time of first diagnosis and at time of index surgery. Proportion of all evaluated comorbidities (AR, polyps, aspirin sensitivity, diabetes, and depression) were greater at time of first diagnosis in group

TABLE 1. Demographic and comorbid conditions in all groups at time of first diagnosis and at time of index surgery*

	Group 1	Group 2	Group 3	Group 4
Conditions at time of first diagnosis				
N	181	195	292	536
Age, years (mean, 95% CI)	43.2 (41.2–45.1)	41.3 (39.4–43.3)	42.3 (40.9–43.8)	41.1 (40.0–42.3)
Patients with AR (%)	32.6	24.1	23.3	14.2
Male (%)	42.5	46.2	43.8	42.7
Patients with polyps (%)	2.8	2.0	2.3	1.9
Patients with aspirin sensitivity (%)	6.6	4.1	2.7	2.2
Patients with diabetes (%)	9.4	6.7	8.2	4.1
Patients with depression (%)	11.0	10.7	9.5	4.4
Conditions at time of surgery				
Age, years (mean, 95% CI)	44.6 (42.6–46.5)	43.8 (42.0–45.8)	45.8 (44.3–47.3)	45.6 (45.2–47.5)
Patients with AR (%)	58.5	60.5	66.4	58.4
Patients with polyps (%)	21.50	15.40	15.40	15.30
Patients with aspirin sensitivity (%)	10.50	10.20	10.90	11.40
Patients with asthma (%)	9.40	12.80	18.20	22.40
Patients with Samter's triad (%)	0.60	0.50	0.30	0.40
Patients with diabetes (%)	12.10	9.70	14.40	11.20
Patients with depression (%)	12.10	18.90	17.10	13.20

*At time of first diagnosis, no patients had asthma because asthma was an exclusion criterion for the study; therefore, no patients had Samter's triad. (Because there is no specific diagnosis for Samter's triad, patients were determined as having the condition if they had concurrent asthma, polyps, and aspirin sensitivity).
AR = allergic rhinitis; CI = confidence interval.

1 versus group 4. At time of first diagnosis, group 4 had the lowest rate of comorbidities. There were no significant differences in age, the average ages at time of first diagnosis being around 40 years.

At time of surgery, comorbidity rates had increased in all groups and for all comorbid conditions. Asthma increased from 0% (exclusion criteria) at time of first diagnosis, to 9.4% at time of surgery for group 1. Between groups 1 and 4, the increase in patients with asthma was near-linear, with an ~3% to 5% increase in patients with asthma per group, reaching 22.40% asthmatics in group 4.

The yearly incidence of patients presenting with a new asthma diagnosis was evaluated. For this analysis, all groups were consolidated and time to asthma was defined based on number of years from first diagnosis and also based on pre- vs post-index surgery timing. Figure 1 shows changes in percentages of patients with asthma diagnoses. Preoperatively, the average yearly incidence of patients with new asthma diagnoses was 5.93% (95% CI, 4.56% to 7.66%) in the AR group and 4.15% (95% CI, 3.56% to 4.82%) in the non-AR group. Using a Fisher's exact test, the difference in average incidences was significant (2-tailed $p = 0.0257$). Postoperatively, the incidence of new cases was 0.80% (95% CI, 0.03% to 3.06%) in the

AR group and 0.52% (95% CI, 0.19 to 1.26) in the non-AR group.

To better understand progression of asthma-like symptoms in ongoing, medically recalcitrant CRS, a time-to-asthma event was constructed from time of first diagnosis to time of index surgery for group 4. Group 4 only was selected for this analysis as it had the longest preoperative time period, ie, period of unoperated CRS, thus allowing for longest comparison between AR and non-AR patients. Figure 2 shows the Kaplan-Meier curve for patients with and without AR. The 95% CI bands were included to highlight statistical differences. As shown in this figure, progression of asthma-like symptoms was consistent over time with AR patients presenting with greater risk than patients without AR. This finding was significant (log rank test p value: 0.0072). To assess the impact of AR and other potential variables, a proportional hazards analysis was conducted. The maximum likelihood estimates for AR, gender, and age (for AR: $\chi^2 = 0.540$, $p = 0.016$, hazard ratio 1.716 [95% CI, 1.103 to 2.669]; for gender: $\chi^2 = 2.03$, $p = 0.154$, hazard ratio 1.312 [95% CI, 0.903 to 1.906]; and for age: $\chi^2 = 1.47$, $p = 0.225$, hazard ratio 0.992 [95% CI, 0.980 to 1.005]) confirming that AR significantly increased risks of asthma but gender and age did not.

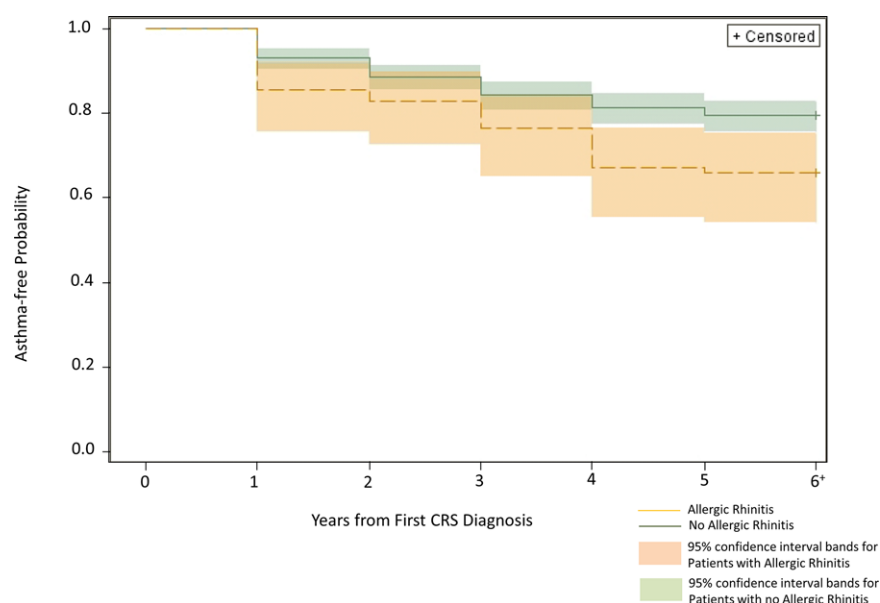


FIGURE 1. Average yearly incidence of patients presenting with new diagnoses of asthma, based on concurrent AR. Comparatively: yearly incidence of asthma in at-risk general adult population was estimated at 0.38%.¹¹ Error bars indicate 95% confidence intervals of the means. Asterisks indicate significance. AR = allergic rhinitis.

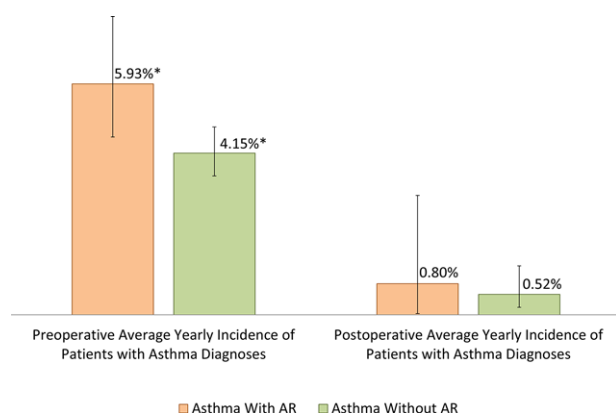


FIGURE 2. Time-to-asthma Kaplan-Meier curve, for patients with and without AR in group 4. This group was selected for this analysis as it had the longest pre-ESS period, thus allowing for comparison of incidence of asthma in the AR vs non-AR population. The 95% confidence interval bands are indicated. Risk of developing asthma-like symptoms was significantly greater in AR vs non-AR patients ($p = 0.0072$). AR = allergic rhinitis; ESS = endoscopic sinus surgery.

To further evaluate whether surgery may have a disease-modifying effect, the percentage of patients with asthma diagnoses at the latest available time point for group 1 (year 2 post-ESS, equivalent to year 4 post-first diagnosis for this cohort) was compared to the percentage of patients with asthma in group 4, at year 4 post-first diagnosis. For the patients in group 4, this time point was between 0 and 1 year pre-ESS, because they all had operations between 4 and 5 years post-first diagnosis. Figure 3 shows the progression of asthma in both groups. At that time, 9.4% patients in group 1 vs 20.7% patients in group 4 had had a diagnosis of asthma. This difference was significant ($p = 0.0005$).

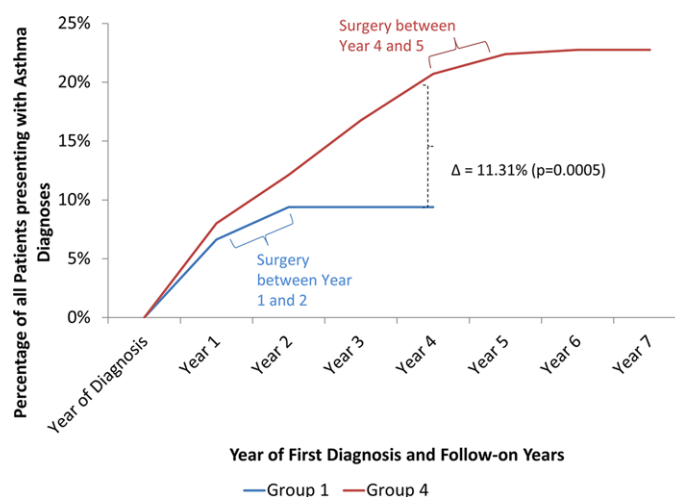


FIGURE 3. Percentage patients with an asthma diagnosis, from time of first diagnosis onward.

Discussion

This study was designed to explore the impact of ongoing, medically-recalcitrant CRS on the development of asthma. To identify patients with ongoing, medically recalcitrant CRS, patients had to be treated with medical management for CRS and despite those treatments, had to eventually undergo surgery. The time period from first CRS diagnosis to surgery was defined as the “ongoing, medically recalcitrant” CRS period. All patients in the selected cohort underwent surgery. This criterion was necessary to ensure: (1) a minimal threshold of disease severity across groups, regardless of timing to surgery—all patients were severe enough to undergo surgery; and (2) to increase

diagnostic accuracy for CRS, because this cohort would have had endoscopy as part of their diagnostic workup. The progression of respiratory comorbidities was therefore tracked in all patients based on their time of first diagnosis—first time sinus/polyposis diagnosis—and after surgery.

The results of our study indicate that with ongoing, medically recalcitrant CRS, patients that initially did not have any asthma diagnosis incurred more than 5% risk per year of developing symptoms that would lead to a diagnosis of asthma. For patients waiting 4 to 5 years until surgery, the risk of being diagnosed with asthma from time of first diagnosis to index surgery ranged from 20.5% for patients without AR to 34.2% for patients with AR, as shown in the Kaplan-Meier curve (Fig. 2). These rates are relatively high, considering that in the United States the overall prevalence of asthma in 2013 reached 6.2% for males and 8.3% for females¹⁰ and yearly prevalence in at-risk adults was estimated at 0.38%.¹¹ In our study, there was a slight trend for lower risk for males but this difference was not significant—the impact of AR playing a much more important role in the risk of being diagnosed with asthma.

Our study did not include patients that had an asthma diagnosis at time of first diagnosis. At that time point, patients in group 1 had significantly greater respiratory comorbidities than patients in group 4. This difference may explain the quicker transition to surgery, whereas all other groups were more likely to wait. This finding may validate other research that suggests that patients may self-select for surgery based on overall well-being.¹²

The findings of this study are intriguing for several reasons. First, it provides large-scale evidence that further supports the 1 airway–1 disease hypothesis and demonstrates the potentially progressive relationship between upper and lower respiratory disease. The increased risk of developing asthma years after medically recalcitrant CRS (and AR) may be the result of a prolonged unchecked inflammatory burden of the upper airway. Second, our results suggest that (early) sinus surgery may play a role in effectively interfering with the progression of this inflammatory march toward more severe respiratory disease (ie, asthma). We find this progressive relationship between unchecked CRS and asthma thought-provoking and similar to the growing evidence that early immunotherapy can reduce the risk of development of asthma in allergic and asthma-prone children.¹³

The findings of this study dovetail with prior work by our group, which showed that early surgical intervention after the diagnosis of CRS was also associated with a significant reduction in healthcare utilization and better outcomes than delayed intervention.^{3,5} Although more work needs to be done in this arena, there appears to be growing evidence in favor of early surgical intervention in CRS, particularly in patients who also have AR. At time of first diagnosis, very few patients overall were identified as having polyps. This may be because, at that time, many patients had only been seen by primary care physicians and

polyps may not have been visible prior to more extensive clinical evaluation by specialists and/or surgery. At time of surgery, however, between 15% and 20% patients across all groups were identified as having polyps. This finding is consistent if not slightly lower than found in a previous study and may be because the cohort identified here excluded patients that had asthma at time of first diagnosis, and thus focused on patients who may overall have been less severe.^{14,15}

In our study, patients were defined as having asthma if they had at least 1 occurrence of a primary or secondary diagnosis of asthma. Early diagnosis of asthma is a complex process¹⁶ and is often rendered based on symptoms only, without complete diagnostic evaluations. We did not evaluate any other subjective criteria for asthma and, therefore, it is very possible that a proportion of patients in the “asthma” group only presented with asthma symptoms.

Our study also did not evaluate possible remission from asthma diagnoses postsurgery. Future research could evaluate subjective diagnostics and asthma-specific drug utilization to determine both incidences of new diagnosis and remission from symptoms.

Timing of other diagnoses specific to sinus disease was also revealing: polyps and aspirin sensitivity were rarely identified at time of first diagnosis. However, by time of surgery, a significant increase in these 2 diagnoses was noticed, probably because from first diagnosis to surgery patients underwent thorough evaluations that identified these comorbidities.

This study has a number of important limitations. Asthma being an anesthesia risk, it may have been increasingly diagnosed preoperatively than postoperatively, as it increases surgical risk factors. Also, all analyses were based on use of database entries and as such were subject to inaccurate coding. Although coding errors do occur, the significant size of the database may compensate for such errors. Our analyses also looked at relative changes and thus were less subject to potential systematic errors that would affect absolute findings. An additional limitation relates to the preoperative and postoperative period: in our study, patients had at most 5 years preoperative and 2 years postoperative medical histories; and whereas no patients had “prior surgery” within that time frame, it is possible that they may have had surgery before that time period. This time frame was selected to provide an initial assessment of change—particularly preoperatively, to study the progression of disease—while maintaining a relatively large patient cohort, because increasing the requirement for complete preoperative and postoperative history in the database would limit the number of available patients. Postoperatively, the short period of time was also selected because others have shown that postoperative outcomes of functional ESS (FESS) appear stable beyond 6 months follow-up; thus, a 6-month postoperative period is often considered sufficient to estimate long-term outcomes¹⁷; however, to truly evaluate the impact of treatments and the natural

history of medically recalcitrant chronic diseases, longer periods before and after surgery may be required.

Conclusion

Ongoing, medically recalcitrant CRS appears to be associated with an increased risk for being diagnosed with asthma. Earlier management of CRS with surgery appears to be associated with a reduction in the risk of developing asthma and further supports the potential that surgery may play a role in disease modification of common airway inflammatory respiratory disease. This risk was significantly

greater for patients with CRS and AR at the time of their first sinusitis/polypoid diagnosis. ④

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