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Elucidating the Real-World Burden of Chronic Rhinosinusitis With Nasal Polyps in Patients in the USA

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Abstract

Objective. To characterize healthcare burden, treatment patterns, and clinical characteristics associated with chronic rhinosinusitis with nasal polyps (CRSwNP).

Study Design. Retrospective cohort.

Setting. Real-world study using US health insurance claims database.

Methods. Adults with ≥1 CRSwNP diagnosis (index date: first claim for nasal polyps [NPs] between January 1, 2008, and March 31, 2019) and continuous health insurance coverage for ≥180 days preindex (baseline) and postindex were included. Follow-up spanned from index to the earliest of disenrollment, death, or data end. Assessments included patient demographics, comorbidities, and blood eosinophil count at baseline, healthcare resource utilization (HCRU), and costs during follow-up in the overall population and stratified by number of surgeries.

Results. Of the 119,357 patients who met the inclusion criteria, 33,748 (28%) had ≥1 surgery during follow-up, among whom 3262 (9.7%) had ≥2 surgeries. At baseline, patients with ≥1 vs no NP surgeries had a greater comorbidity burden; a higher proportion of patients had comorbid asthma (37.8% vs 21.8%) and blood eosinophil count ≥300 cells/μL (42.6% vs 38.1%). During follow-up, patients with NP surgeries had higher all-cause and CRSwNP-related HCRU and costs than patients without NP surgery. All-cause healthcare costs per person per year increased with the number of surgeries during follow-up (no surgery, $10,628; ≥1 surgery, $20,747; ≥2 surgeries, $26,969).

Conclusion. Patients with CRSwNP and surgery had a greater disease burden than those without surgery, with higher HCRU and costs, and were more likely to have comorbid conditions (most commonly asthma) and elevated blood eosinophil count, indicating a subset of patients with recalcitrant CRSwNP.

Keywords

real world, nasal polyps, asthma, healthcare resource utilization, claims

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Nasal polyps (NPs), inflammatory outgrowths of sinonasal tissue, are considered a defining feature of a subgroup of chronic rhinosinusitis (CRS): CRS with NP (CRSwNP).[1-3] CRS affects 3% to 27% of the adult population in Europe and the United States (depending on the definition used),[4-7] while population estimates of the prevalence of CRSwNP vary from 1.1% in the United States to 4.3% in Finland.[4,8] Symptoms of CRSwNP include loss of smell, nasal congestion or obstruction, facial pain or pressure, nasal discharge, and postnasal drip.[9] CRSwNP negatively affects quality of life (QoL), affecting emotional state, sleep, and daily activities, including loss of work and productivity.[1,2,4,10-12] CRSwNP is also associated with several type 2 inflammatory comorbidities, particularly asthma, aspirin hypersensitivity, and other atopic diseases.[12-15]

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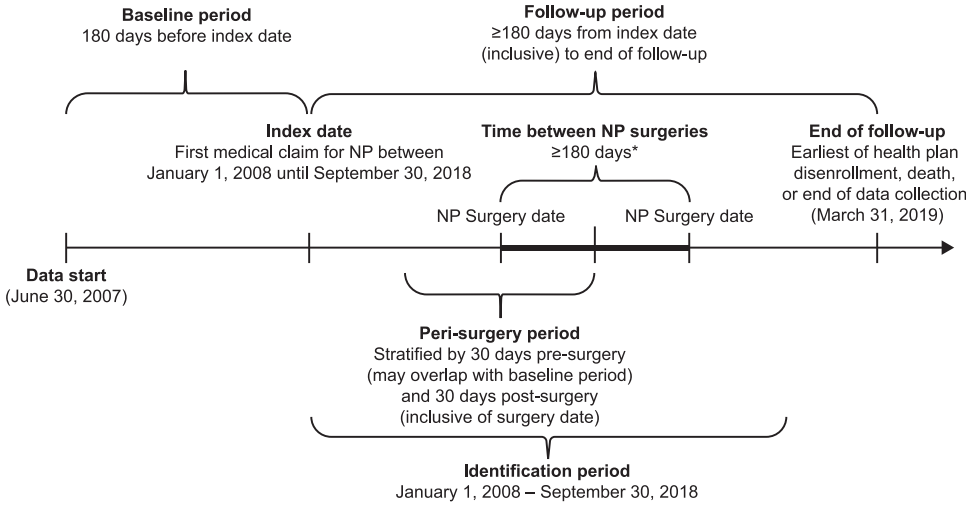


Figure 1. Study design. *Nasal polyp (NP) surgeries <180 days apart were not considered new surgeries. If a surgery occurred within 180 days of the previous surgery, the minimum of 180 days surgery-free time restarted.

Standard of care for CRSwNP includes intranasal corticosteroids, saline nasal douching, and short courses of systemic corticosteroids.[9] In more severe cases, macrolide antibiotics, drug-eluting stents, and biologics may be used.[2,3,9,16] When therapies fail to control chronic disease, surgery is considered, ranging from simple polypectomy to radical nasalization; endoscopic sinus surgeries (ESSs) are also common.[16] Surgical and medical interventions can manage CRSwNP symptoms in many cases; however, despite postoperative medical treatment, some patients experience recalcitrant disease.[9] In this population, CRSwNP often recurs after surgery, leading to multiple surgeries, numerous courses of systemic corticosteroids, and worsening QoL. For example, a multicenter North American study found that 40% of patients with recalcitrant CRSwNP experience recurrence within 18 months of ESS via follow-up endoscopy,[17] and a meta-analysis reported an overall ESS revision rate of 18.6% over an average follow-up of 7.4 years; revision rates increased with the presence of allergic fungal rhinosinusitis and comorbid aspirin-exacerbated respiratory disease (AERD) or asthma.[18] High rates of post surgery NP recurrence and need for repeat surgery are also linked to high blood and/or tissue eosinophil counts.[19-23] These studies indicate that a subset of patients with recalcitrant disease may be inadequately controlled by current therapies; however, investigation of the characteristics and medical and economic burden of patients with CRSwNP is needed to characterize this unmet need.

Using data from a large US health insurance claims database, we aimed to characterize the demographics, clinical characteristics, healthcare resource utilization (HCRU), and costs in patients with CRSwNP, with or without surgery. In addition, the prevalence of CRSwNP was estimated. The objective of the study was to enhance our understanding of the real-world burden of disease among patients with CRSwNP, in order to identify patients with high unmet need who may warrant additional therapeutic intervention.

Methods

Study Design

This retrospective cohort study used data from Optum Clinformatics Data Mart (June 30, 2007– March 31, 2019), a deidentified health insurance claims database containing commercial and Medicare Advantage health plan data covering 12 to 14 million annual lives across the United States. Patients with CRSwNP were identified using medical diagnosis codes for NPs (International Classification of Diseases [ICD]-9-CM: 471.x; ICD-10-CM: J33.x). Patients with a CRSwNP diagnosis between January 1, 2008, and September 30, 2018 (identification period), were included. The index date was the date of the first CRSwNP diagnosis during the identification period. The baseline period was the 180 days prior to the index date, which could extend back to June 30, 2007. The follow-up period spanned from the index date (inclusive) until the earliest of health plan disenrollment, death, or March 31, 2019; included patients were required to have ≥180 days of follow-up (**Figure 1**). For patients with NP surgery during follow-up, data were collected for the 30 days pre- and post surgery (peri surgery period). The surgery date was included in the post surgery period. Evaluation of study outcomes post surgery was performed for patients with sufficient follow-up.

Potential procedure codes indicating NP removal surgery were identified by expert review and classified as ‘‘NP surgery’’ or ‘‘could include NP surgery’’ (see Supplemental Table S1 in the online version of the article). In the main analysis, NP surgeries were identified using both ‘‘NP surgery’’ and ‘‘could include NP surgery’’ classifications; codes classified as ‘‘could include NP surgery’’ were not counted as NP surgeries if a diagnosis of CRS occurred on the same day, unless a diagnosis of NP was also present. New surgeries required ≥180 days surgery-free time between surgeries. Surgeries occurring within 180 days of the initial surgery were considered as near-term repeat surgeries and the ≥180 days of surgery-free duration was restarted from the date of the most

Table 1. Prevalence of Nasal Polyps Among Commercially Insured US Adults.

	Prevalence from Optum sample		Standardized prevalence using 2018 US census data
Characteristic	n	Prevalence per 100,000 (95% CI)	Prevalence per 100,000 (95% CI)
Sex			
Male	13,037	233 (198,269)	215 (181,249)
Female	9577	157 (128,186)	158 (129,187)
Age group, years			
18–20	353	95 (1,190)	95 (1,190)
21–44	5060	147 (109,184)	147 (109,184)
45–64	7674	231 (186,276)	230 (184,275)
65–74	5658	229 (177,281)	233 (180,286)
75–84	3049	208 (142,273)	210 (144,275)
≥85	820	137 (50,223)	138 (51,225)
Overall	22,614	194 (171,216)	186 (163,208)

recent surgery. Near-term repeat surgeries were identified using the same procedure codes as new surgeries.

This study used data collected from patients' interactions with their healthcare insurance provision. The analysis used fully deidentified retrospective data; this is not classified as research involving human participants (defined by 45 CFR 46.102(f)(2)). Therefore, institutional review board approval and informed consent were not required from Optum.

Main Study Population

Eligible patients were ≥18 years of age at index date, with ≥1 CRSwNP diagnosis within the study period and ≥180 days of continuous enrollment prior to and after the index date.

Prevalence Estimates

The prevalence of CRSwNP in 2018 was calculated within the Optum Clinformatics Data Mart database. The numerator was defined as patients with continuous enrollment throughout 2018 with ≥1 diagnosis of CRSwNP (during 2018). The denominator was defined as patients with continuous enrollment throughout 2018. The prevalence of CRSwNP in 2018 was standardized to the US national population using 2018 US Census data. The proportion with CRSwNP was calculated by sex and age categories; this proportion was then applied to the 2018 US Census population to estimate the expected number of people with CRSwNP under the national distribution of sex and age.

Variables and Outcomes

Patient demographics at index and clinical characteristics during the baseline period, including comorbidities identified by ICD-9/10-CM diagnosis codes, were reported and stratified by new NP surgery number (no surgery, ≥1, or ≥2). All-cause and CRSwNP-related (medical service claim associated with a primary diagnosis of CRSwNP or NP surgery) HCRU and costs were calculated during the follow-up and the peri surgery periods. In addition, surgery rates and median time between new NP surgeries were assessed.

Availability of baseline blood eosinophil counts, frequency of eosinophil thresholds, and geometric mean blood eosinophil counts were stratified by new NP surgery number (no surgery, ≥1, ≥2) during follow-up. The proportions of patients with oral corticosteroid (OCS) usage 30 days before eosinophil measurement and the baseline characteristics of patients with and without ≥1 available blood eosinophil count were also reported.

This study also described patients with ≥1 new NP surgery, with and without asthma during baseline. Baseline clinical characteristics, HCRU and costs during follow-up, costs and treatment use during the peri surgery period, and surgery rates of these patients were reported.

Statistical Analyses

All variables and outcomes were analyzed descriptively. Means, medians, and proportions were calculated with standard deviations, interquartile ranges, and 95% CI, where appropriate. Costs were inflation adjusted to 2018 US dollars based on the medical care component of the Consumer Price Index. Surgery rates stratified by surgery number were calculated by Kaplan-Meier analysis.

To assess the reliability of NP surgery classifications, 2 sensitivity analyses were conducted: an analysis using only ESS procedure codes to identify NP surgeries and an analysis in which procedure codes classified as ''could include NP surgery'' were only included as NP surgery when a NP diagnosis occurred on the same day. To assess data robustness and potential loss of information due to patient disenrollment, a third sensitivity analysis of rate and median time between surgeries for patients with a ≥36-month follow-up was performed.

Results

Prevalence of CRSwNP Among Commercially Insured US Adults

In the Optum database, the age- and sex-standardized prevalence of NP was 186 cases per 100,000 individuals (**Table 1**).

Prevalence was highest in males and in the 45- to 64-year and 65- to 74-year age groups.

Study Population

Of 119,357 eligible patients with CRSwNP identified, 85,609 (71.7%) had no NP surgery, while 33,748 (28.3%) had ≥1 surgery, over an average of 38.7 months of follow-up. Among patients who had surgery, 3262 (9.7%) had ≥2 surgeries.

Mean age at index was 53.0 years; patients with ≥1 or ≥2 NP surgeries were very slightly younger than those with no surgery. Mean Quan-Charlson comorbidity index (CCI) score during baseline was 0.40 for patients with no surgery and increased with number of surgeries (≥1 surgery, 0.52; ≥2 surgeries, 0.59). Asthma, allergic rhinitis, allergic asthma, hypertension, chronic pulmonary disease, sleep-wake disorders, depressive disorders, anxiety disorders, and chronic obstructive pulmonary disease (COPD) were all present with prevalences ≥5% and all were more frequent in patients with surgery than those without. For example, asthma was present in 21.8%, 37.8%, and 52.1% of patients with no, ≥1, and ≥2 surgeries during follow-up, respectively (**Table 2**). The same pattern was seen among less prevalent comorbidities, which included obesity, eosinophilic esophagitis, severe asthma, inflammatory bowel disease, AERD, and eosinophilic granulomatosis with polyangiitis (EGPA).

All-Cause and CRSwNP-Related HCRU and Costs

During the follow-up period, patients with NP surgeries had higher all-cause and CRSwNP-related HCRU and costs than those without NP surgeries. All-cause healthcare costs per person per year increased with number of surgeries (no surgery, $10,628; ≥1 surgery, $20,747; ≥2 surgeries, $26,969) (**Table 3**). As expected, all-cause and CRSwNP-related HCRU and healthcare costs were higher in the post surgery (which included the surgery day) than the pre surgery period (**Table 4**), a trend consistent across hospitalizations, emergency room visits, and outpatient visits. Most HCRU and costs were incurred in the outpatient setting, accounting for 68.6% and 86.2% of all-cause total healthcare costs in the 30-days pre- and post surgery, respectively.

CRSwNP-Related Treatments and Surgery Complications

The most common CRSwNP-related treatment during the peri–first surgery period was OCS, used by 24.7% and 21.8% of patients in the 30-days pre- and post surgery, respectively (**Table 5**). Injectable corticosteroid use was more common post surgery than pre surgery, while use of mometasone furoate stents was similar pre- and post surgery. Peri–second surgery results were similar to first surgeries and are described in Supplemental Table S2 (in the online version of the article).

Surgery

Most NP surgeries occurred in an outpatient hospital setting; however, the proportion of surgeries performed in this setting reduced with increasing surgery number (78.4%, 53.6%, and 40.9% of first, second, and third surgeries, respectively; see Supplemental Table S3 in the online version of the article). Kaplan-Meier analyses of the time to first, second, and third surgery demonstrate the changing rates of surgery among patients requiring multiple surgeries. The incidence (ie, probability) of second or third surgeries within 36 months of the previous surgery was 11.2% (among patients with ≥1 surgeries) and 29.0% (among patients with ≥2 surgeries), respectively (**Figure 2**). Among patients with multiple surgeries, median time between surgeries decreased from 18.4, 16.0, and 15.3 months after the first, second, and third surgeries among patients with ≥2, ≥3, and ≥4 surgeries, respectively (**Table 6**). Overall, 57.3% of patients who underwent surgery had ≥1 near-term repeat surgery within 180 days of a first surgery; the proportion of patients who underwent near-term repeat surgery decreased with increasing surgery number (**Table 6**).

Blood Eosinophil Count

Baseline blood eosinophil count data were available for 13.7% of 119,357 patients included in the study; geometric mean blood eosinophil count increased with increasing surgery number, as did the proportion of patients with blood eosinophil count ≥300 cells/μL (no surgery, 38.1%; ≥1 surgery, 42.6%; ≥2 surgeries, 48.0%; **Table 2**). Patients with vs without blood eosinophil count data had a higher mean Quan-CCI score (see Supplemental Table S4 in the online version of the article).

Patients With Comorbid Asthma and ≥ 1 Surgery

Among patients with ≥1 surgery (n = 33,748), comorbid asthma was present in 37.8% of patients at baseline. Relative to the no-asthma cohort, the asthma cohort had more female patients (49.4% vs 36.7%), a higher mean Quan-CCI score (0.81 vs 0.35) (see Supplemental Table S5 in the online version of the article), and higher CRSwNP-related total healthcare costs ($6186 vs $5795) (see Supplemental Table S6 in the online version of the article). During the 30-days pre– and post–first surgery, CRSwNP-related treatments were slightly more common in the asthma cohort than the no-asthma cohort (eg, the proportion of patients receiving OCS pre surgery: 30.7% and 21.1% with asthma vs no asthma and post surgery: 26.4% and 19.0%, respectively), and CRSwNP-related HCRU and costs were consistently higher in the asthma cohort than the no-asthma cohort (see Supplemental Table S7 in the online version of the article). Incidences of second and third surgeries were slightly higher in the asthma cohort than the no-asthma cohort (see Supplemental Table S8 in the online version of the article). The median time between first and second surgeries was longer in the asthma (19.9 months) than the no-asthma cohort (16.4 months), and the proportion of near-term repeat surgeries was higher in the asthma than the no-asthma cohort (first surgery: 60.6% and 55.3%; second surgery: 53.6% and 44.1%; third surgery: 53.5% and 41.0%, respectively) (data not shown).

Sensitivity Analyses

The results of sensitivity analyses were consistent with the main analysis and are described in the Supplementary Results

Table 2. Baseline Demographics and Clinical Characteristics by Number of Surgeries During Follow-up.

Characteristic	Overall (N = 119,357)	Number of NP surgeries during follow-up		
		No surgery (n = 85,609)	≥1 surgery (n = 33,748)	≥2 surgeries (n = 3262)
Follow-up period,[a] mo				
Mean (SD)	38.7 (30.1)	37.2 (29.2)	42.5 (31.9)	62.8 (34.3)
Median (Q1, Q3)	29.0 (15.4, 53.7)	27.7 (14.8, 51.1)	33.1 (17.1, 59.8)	57.3 (34.7, 86.7)
Age,[b] mean (SD), y	53.0 (16.7)	53.5 (16.9)	51.6 (16.3)	51.2 (15.6)
Female,[b] No. (%)	53,188 (44.6)	39,183 (45.8)	14,005 (41.5)	1504 (46.1)
Region,[b] No. (%)				
South	49,290 (41.3)	34,873 (40.7)	14,417 (42.7)	1481 (45.4)
West	26,694 (22.4)	19,393 (22.7)	7301 (21.6)	721 (22.1)
Midwest	27,207 (22.8)	19,258 (22.5)	7949 (23.6)	691 (21.2)
Northeast	15,644 (13.1)	11,701 (13.7)	3943 (11.7)	351 (10.8)
Unknown	522 (0.4)	384 (0.4)	138 (0.4)	18 (0.6)
Insurance plan, No. (%)				
Commercial[b]	86,063 (72.1)	60,742 (71.0)	25,321 (75.0)	2470 (75.7)
Medicare[b]	33,294 (27.9)	24,867 (29.0)	8427 (25.0)	792 (24.3)
Quan-CCI score, mean (SD)	0.44 (1.00)	0.40 (0.99)	0.52 (1.01)	0.59 (1.00)
Comorbidities, No. (%)				
Respiratory				
Asthma	31,440 (26.3)	18,681 (21.8)	12,759 (37.8)	1700 (52.1)
Allergic rhinitis	24,400 (20.4)	12,927 (15.1)	11,473 (34.0)	1318 (40.4)
Allergic asthma	14,475 (12.1)	7976 (9.3)	6499 (19.3)	976 (29.9)
Chronic pulmonary disease	13,464 (11.3)	8002 (9.3)	5462 (16.2)	789 (24.2)
COPD	5959 (5.0)	3908 (4.6)	2051 (6.1)	209 (6.4)
Severe asthma (GINA 4 or 5)[c]	1412 (1.2)	781 (0.9)	631 (1.9)	107 (3.3)
AERD	781 (0.7)	454 (0.5)	327 (1.0)	48 (1.5)
EGPA[d]	41 (0.03)	24 (0.03)	17 (0.05)	3 (0.09)
Nonrespiratory				
Hypertension	20,224 (16.9)	13,061 (15.3)	7163 (21.2)	801 (24.6)
Sleep-wake disorders	9587 (8.0)	5548 (6.5)	4039 (12.0)	384 (11.8)
Depressive disorders	6824 (5.7)	4270 (5.0)	2554 (7.6)	263 (8.1)
Anxiety disorders	6472 (5.4)	4120 (4.8)	2352 (7.0)	217 (6.7)
Eosinophilic esophagitis	2081 (1.7)	1316 (1.5)	765 (2.3)	90 (2.8)
Inflammatory bowel disease	708 (0.6)	433 (0.5)	275 (0.8)	32 (1.0)
Atopic dermatitis	615 (0.5)	397 (0.5)	218 (0.6)	19 (0.6)
Herpes zoster	518 (0.4)	331 (0.4)	187 (0.6)	17 (0.5)
Blood eosinophil count,[e] cells/μL				
Patients with ≥1 measurement, No. (%)	16,409 (13.7)	11,649 (13.6)	4760 (14.1)	481 (14.7)
Geometric mean (log SD)	220.2 (0.71)	215.6 (0.70)	231.7 (0.71)	249.3 (0.77)
Categories, No. (%)				
<150	5776 (35.2)	4207 (36.1)	1569 (33.0)	158 (32.8)
≥150	10,633 (64.8)	7442 (63.9)	3191 (67.0)	323 (67.2)
≥150-<300	4173 (25.4)	3009 (25.8)	1164 (24.5)	92 (19.1)
≥300	6460 (39.4)	4433 (38.1)	2027 (42.6)	231 (48.0)
OCS use 30 days prior to blood eosinophil measurement, No. (%)	1068 (6.5)	507 (4.4)	561 (11.8)	75 (15.6)

Abbreviations: AERD, aspirin-exasperated respiratory disease; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; EGPA, eosinophilic granulomatosis with polyangiitis; GINA, Global Initiative for Asthma; ICS/LABA, Inhaled corticosteroids/ long-acting β_2 agonists; NP, nasal polyp; OCS, oral corticosteroid; Q, quartile.

[a]The follow-up period spans from the index date (inclusive) until the earliest of health plan disenrollment, death, or end of data availability.

[b]Evaluated at the index date.

[c]GINA 4 was defined as ≥1 dispensing of a medium-high dose of ICS/LABA. GINA 5 was defined as ≥1 dispensing of a high-dose of ICS/LABA and ≥1 dispensing of tiotropium or a biologic.

[d]While EGPA is multisystemic small/medium-vessel vasculitis, asthma is a key piece in the diagnostic criteria and so the closest categorical alignment for EGPA was respiratory comorbidities.

[e]Identified with Logical Observation Identifiers Names and Codes 26449-9, 713-8, and 714-6. The closest measurement to the index date during baseline was used. For those with multiple measurements on the closest day, the mean was taken.

Table 3. HCRU and Costs During the Follow-up Period by Number of Surgeries During Follow-up.

Characteristic	Overall (N = 119,357)	Number of NP surgeries during follow-up		
		No surgery (n = 85,609)	≥1 surgery (n = 33,748)	≥2 surgeries (n = 3262)
HCRU, PPPY				
All-cause				
Hospitalizations	0.116	0.107	0.136	0.158
ER visits	0.743	0.610	1.040	1.286
Outpatient visits	11.642	9.755	15.829	19.560
Other visits	2.199	2.017	2.601	3.251
CRSwNP related[a]				
Hospitalizations	0.002	<0.001	0.006	0.010
ER visits	0.019	0.005	0.050	0.079
Outpatient visits	0.375	0.126	0.928	1.279
Other visits	0.032	0.013	0.077	0.118
Healthcare costs, $US 2018, PPPY				
All-cause				
Total healthcare costs[b]	13,772	10,628	20,747	26,969
Total medical costs	11,608	8849	17,728	21,975
Hospitalizations	3002	2872	3292	3825
ER visits	1062	936	1342	1548
Outpatient visits	6611	4319	11,697	14,698
Other visits	932	723	1397	1903
Pharmacy costs	2164	1779	3019	4994
CRSwNP related[a]				
Total healthcare costs[b]	1931	117	5956	7254
Total medical costs	1854	56	5843	7048
Hospitalizations	66	8	194	330
ER visits	35	5	103	118
Outpatient visits	1643	40	5200	6163
Other visits	110	4	347	438
Pharmacy costs	77	61	113	206

Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyps; ER, emergency room; HCRU, healthcare resource utilization; NP, nasal polyp; PPPY, per patient per year.

[a]A medical service claim was considered CRSwNP related if it was associated with a primary diagnosis of CRSwNP or an NP surgery. A pharmacy claim was considered CRSwNP related if it was a claim for a CRSwNP-related treatment prescription.

[b]Due to rounding, cost components may not add up to the total.

(shown in Supplemental Tables S9, S10, S11, S12, and S13 in the online version of the article).

Discussion

This real-world characterization of US patients with CRSwNP included a large sample of patients to assess burden of disease. The results indicated that patients with CRSwNP who required NP surgery were very slightly younger, had more comorbidities, and had higher blood eosinophil counts at baseline than patients not requiring surgery during follow-up. These trends were more pronounced with increasing number of surgeries during follow-up (eg, 52.1% of patients with ≥2 surgeries had comorbid asthma vs 26.3% with no surgeries). The trend for increased burden of comorbidities among patients with NP surgery was particularly pronounced among the respiratory comorbidities, with asthma, allergic rhinitis, chronic pulmonary disease, AERD, and EGPA all at least twice as prevalent among patients with ≥2 surgeries than among those with no surgery. There was also a ≥50% increase in the prevalence of hypertension, sleep-wake disorders, depressive disorders, eosinophilic esophagitis, and inflammatory bowel disease among patients with ≥1 or ≥2 surgeries than among patients with no NP surgery. The proportion of patients with blood eosinophil count ≥300 cells/μL also increased with increasing number of surgeries, indicating that patients requiring multiple surgeries were more likely to have had baseline eosinophilic inflammation, indicative of type 2 inflammation, associated with their CRSwNP. Several of the identified comorbidities are also associated with type 2 inflammation (eg, asthma and AERD).

These results are consistent with the current understanding of CRSwNP endophenotypes. Studies have shown that type 2 inflammation, with elevated eosinophils and high levels of IL-4, IL-5, and IL-13, is implicated in the pathogenesis

Table 4. HCRU and Costs During the 30-Day Pre- and Post surgery Periods (for First Surgeries) in Patients With ≥1 Surgery.

Characteristic	30-day pre surgery period (n = 33,547)	30-day post surgery period[a] (n = 33,547)
HCRU, mean (SD)		
All-cause		
Hospitalizations	0.01 (0.10)	0.03 (0.17)
ER visits	0.12 (0.52)	0.19 (0.64)
Outpatient visits	2.47 (2.14)	2.99 (2.12)
Other visits	0.26 (0.92)	0.31 (1.00)
CRSwNP-related[b]		
Hospitalizations	<0.01 (0.03)	0.01 (0.12)
ER visits	0.01 (0.09)	0.09 (0.42)
Outpatient visits	0.23 (0.54)	1.74 (1.51)
Other visits	0.02 (0.15)	0.14 (0.48)
Healthcare costs, $US 2018, mean (SD)		
All-cause		
Total healthcare costs	2073 (5985)	18,727 (17,405)
Total medical costs	1818 (5742)	18,442 (17,298)
Hospitalizations	145 (2876)	737 (7457)
ER visits	145 (1300)	449 (3103)
Outpatient visits	1422 (4518)	16,143 (16,028)
Other visits	106 (960)	1114 (5216)
Pharmacy costs	255 (1292)	285 (1155)
CRSwNP-related[b]		
Total healthcare costs	324 (2368)	10,401 (11,945)
Total medical costs	312 (2365)	10,387 (11,944)
Hospitalizations	5 (374)	86 (1599)
ER visits	7 (417)	164 (1665)
Outpatient visits	285 (2263)	9474 (11,766)
Other visits	14 (384)	663 (3714)
Pharmacy costs	12 (122)	14 (82)

Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyps; ER, emergency room; HCRU, healthcare resource utilization; NP, nasal polyp; PPPY, per patient per year.

[a]The date of surgery is included in the post surgery period.

[b]A medical service claim was considered CRSwNP related if it was associated with a primary diagnosis of CRSwNP or an NP surgery. A pharmacy claim was considered CRSwNP related if it was a claim for a CRSwNP-related treatment prescription.

of CRSwNP.[1,3,24-26] Blood eosinophilia was associated with disease recurrence and asthma comorbidity in patients with CRSwNP,[27-30] and comorbid asthma, past surgery, and eosinophilia have all been identified as risk factors for CRSwNP recurrence and future NP surgery.[19-22,31] While blood eosinophil counts were higher at baseline in patients requiring surgery during follow-up than in patients without surgery, the use of OCS within 30 days prior to blood eosinophil count measurement was also higher among patients with surgery. Therefore, the proportion of surgical patients with an eosinophilic phenotype was likely underestimated due to the OCS effects.

Our results also demonstrate that as the number of surgeries a patient undergoes increases, the time interval between surgeries becomes slightly shorter compared with patients with fewer surgeries. In addition, among patients with ≥2 surgeries, the rate of third surgeries at 36 months was equivalent to the rate of first surgeries among the total study population, indicating the ongoing need for further surgery in a subset of patients. These findings are supported by a previous study in which the rate of revision surgery for CRSwNP following ESS was 15.9% over a mean follow-up of 9.7 years.[31] A small subset of patients required multiple revision surgeries, and the time between surgeries decreased with successive surgeries.[31]

Consistent with the current literature of more severe and difficult-to-manage CRSwNP among patients with asthma,[13] we found that patients with comorbid asthma and ≥1 NP surgery had a higher incidence of second and third NP surgeries than patients without asthma. OCS use pre- and post surgery was also higher in patients with asthma than without. Consistent with this increased surgical and medical burden, both all-cause and CRSwNP-related costs were higher among surgical patients with asthma than those without during the post surgery period. Overall, these results suggest there is a subpopulation of patients with severe and difficult-to-treat disease, characterized by clinical traits, such as eosinophilia and comorbid asthma, who require repeated revision NP surgeries at an increasingly frequent rate.

Table 5. CRSwNP-Related Treatments and Surgery Complications During the Pre- and Post surgery Periods (for First Surgeries) in Patients With ≥1 Surgery.

Characteristic	30-day pre surgery period (n = 33,547)	30-day post surgery period[a] (n = 33,547)
CRSwNP-related treatments, No. (%)		
Topical steroids (intranasal sprays/drops)	3149 (9.4)	3814 (11.4)
Mometasone furoate nasal implants (stent)	973 (2.9)	1371 (4.1)
Systemic corticosteroids	9002 (26.8)	9855 (29.4)
Oral corticosteroids	8290 (24.7)	7315 (21.8)
Injectable corticosteroids	1044 (3.1)	3149 (9.4)
Oral antibiotics		
Macrolides	1823 (5.4)	2152 (6.4)
Azithromycin	1201 (3.6)	1480 (4.4)
Clarithromycin	609 (1.8)	645 (1.9)
Erythromycin	50 (0.1)	47 (0.1)
Doxycycline	657 (2.0)	808 (2.4)
Biologics	115 (0.3)	117 (0.3)
CRSwNP-related procedures, No. (%)		
CT scan	7166 (21.4)	6159 (18.4)
Nasal/sinus endoscopy	10,629 (31.7)	1594 (4.8)
Surgery complications, No. (%)		
Infection	—	39 (0.1)
Bleeding	—	211 (0.6)
Cerebrospinal fluid leak	—	74 (0.2)
Deep vein thrombosis	—	139 (0.4)
Associated procedures, No. (%)		
Debridement	—	19 (0.1)
Acquired deformity of the nose[b]	—	482 (1.4)
Septo-rhinoplasty[c]	—	129 (0.4)

Abbreviations: CPT, Current Procedural Terminology; CRSwNP, chronic rhinosinusitis with nasal polyps; CT, computed tomography; HCPCS, healthcare common procedure coding system; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, 10th Revision, Clinical Modification; ICD-10-PCS, International Classification of Diseases, 10th Revision, Procedural Coding System; —, Not applicable. Data on surgery complications and associated procedures were not evaluated for the pre-surgery period.

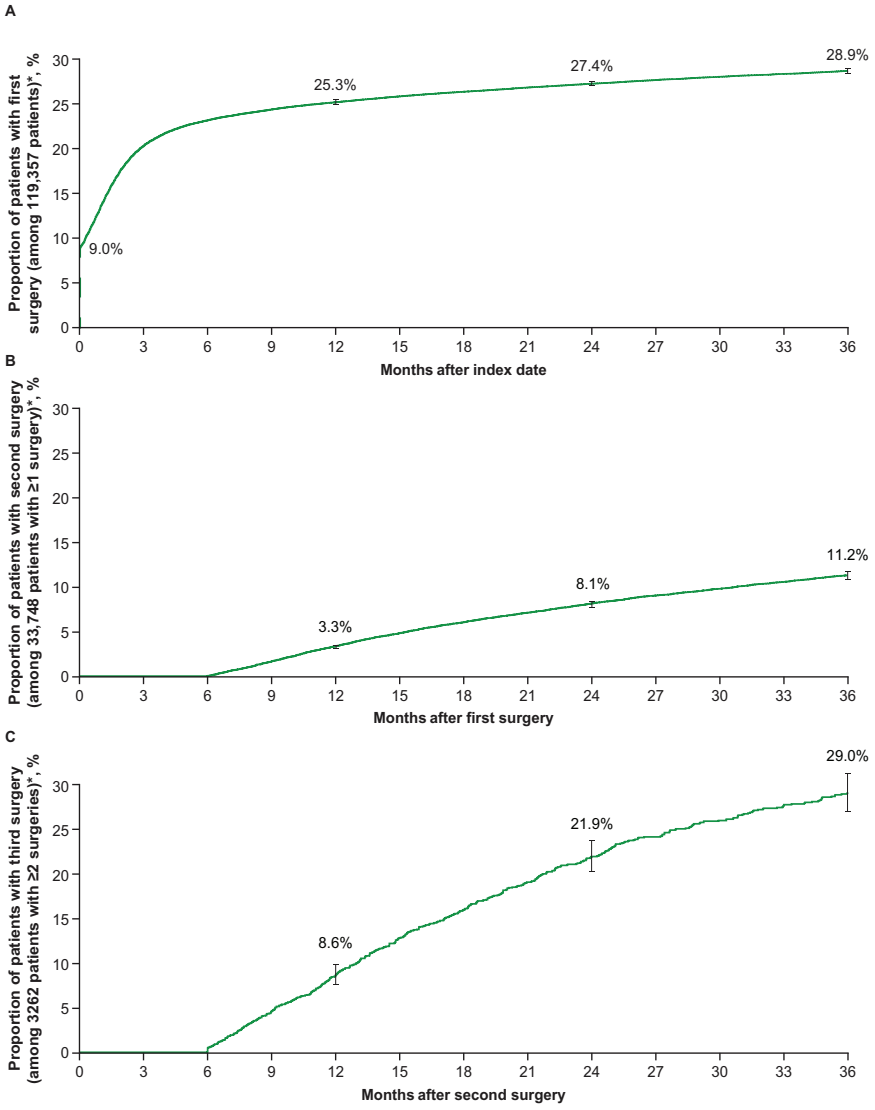
[a]The date of surgery is included in the post surgery period.

[b]Nasal collapse (ICD-9-CM:738.0, ICD-10-CM: M95.0).

[c]Septo-rhinoplasty includes rhinoplasty (CPT: 30400, 30410, 30420, 30435, 30450), nasal bone operation (ICD-10-PCS: 0NWB00Z, 0NWB04Z, 0NWB07Z, 0NWB0JZ, 0NWB0KZ, 0NWB0MZ, 0NWB30Z, 0NWB34Z, 0NWB37Z, 0NWB3KZ, 0NWB3MZ, 0NWB40Z, 0NWB44Z, 0NWB47Z, 0NWB4JZ, 0NWB4KZ, 0NWB4MZ, 0NWBX0Z, 0NWBX4Z, 0NWBX7Z, 0NWBXJZ, 0NWBXKZ, 0NWBXMZ), nasal mucosa and soft tissue operation (ICD-10-PCS: 09WK80Z, 09WK87Z, 09WK8DZ, 09WK8JZ, 09WK8KZ, 09WK8YZ, 09WKX0Z, 09WKX7Z, 09WKXDZ, 09WKXJZ, 09WKXKZ, 09WY00Z, 09WY0YZ, 09WY30Z, 09WY3YZ, 09WY40Z, 09WY4YZ, 09WY7YZ, 09WY8YZ, 09WYX0Z, 09WK00Z, 09WK07Z, 09WK0DZ, 09WK0JZ, 09WK0KZ, 09WK0YZ, 09WK30Z, 09WK37Z, 09WK3DZ, 09WK3JZ, 09WK3KZ, 09WK3YZ, 09WK40Z, 09WK47Z, 09WK4DZ, 09WK4JZ, 09WK4KZ, 09WK4YZ, 09WK70Z, 09WK77Z, 09WK7DZ, 09WK7JZ, 09WK7KZ, 09WK7YZ), and nasal prosthesis (HCPCS: L8040, L8047).

The standardized prevalence of CRSwNP in 2018 among patients in the Optum database (0.186%) was approximately 6-fold lower than a previous estimate in the general US population (1.1%).[4] As our data were based on medical claims, this discrepancy could be due to many individuals with CRSwNP symptoms not seeking medical care in the study year or patients not being represented in this database. In addition, it should be noted that the previous estimate of CRSwNP prevalence was based on self-reported survey data not on medical claims data.[4] Interestingly, a previous retrospective cohort study using electronic health records of 446,480 primary care US patients estimated the incidence of new CRSwNP diagnosis to be 83 per 100,000 person years (0.083%).[15]

This study used data from a large, geographically diverse US health insurance claims database, which allowed access to a large patient cohort, but was accompanied by the usual limitations of a retrospective claims database study. For example, the study relied on diagnosis and procedure codes used for administrative billing purposes. NP surgeries ranged from minor to extensive procedures, and details of the extent of procedures were not captured. For several procedure codes used, it is uncertain whether they were specific for NP surgery. However, the study included patients with CRSwNP, and the surgery identification sensitivity analyses indicate that the study findings are robust to changes in billing and coding of NP surgeries. Furthermore, while a high proportion



*Patients without an NP surgery by the end of their observation period were no longer considered at risk (i.e., censored).
Surgeries ≤180 days from previous surgery were not included.

Figure 2. Incidence of nasal polyp surgery estimated by Kaplan-Meier analysis of time from (A) index date to first surgery, (B) first to second surgery, and (C) second to third surgery.

of surgeries captured required further surgery within 180 days of a prior surgery (considered near-term repeat surgery), this could be due to the procedural codes used to identify NP surgeries. Factors driving the high proportion of near-term repeat surgeries were not investigated. In addition, some patients may have had NP surgery prior to the identification period. A further limitation was that some CRSwNP medications, such as steroid sprays, are available over the counter, and their use may be underreported in this study. Another important consideration is that over the course of the identification period, new options for intranasal corticosteroid delivery, such as mometasone furoate stents, became available. It should also be noted that blood eosinophil count data were not available for all patients in this study, and patients with NP surgery more commonly had these data available. However, overall, the similarity of the results of both the surgery classification and the 36-month follow-up sensitivity analyses to the main analysis suggests the main analysis findings are robust.

In conclusion, we identified a subpopulation of patients with CRSwNP with a high clinical and socioeconomic disease burden. Patients in this subpopulation have high medication use, HCRU, and costs, and they require repeated surgery, indicating suboptimal treatment outcomes with current standard-of-care approaches for some patients. This subpopulation also displays traits of more severe CRSwNP with a higher prevalence of type 2 associated inflammatory comorbidities (including asthma, AERD) and an elevated blood eosinophil count, compared with patients with CRSwNP who do not

Table 6. Time Between NP Surgeries and Near-Term Repeat Surgery Rates.

Time to surgery	Value
Patients with ≥1 surgery	33,748
Time between index and first surgery, mo	
Mean (SD)	5.1 (12.0)
Median (Q1, Q3)	1.1 (0.0, 3.6)
Near-term repeat surgery,[a] No. (%)	19,327 (57.3)
Patients with ≥2 surgeries	3262 (9.7)
Time between index and first surgery, mo	
Mean (SD)	4.8 (10.7)
Median (Q1, Q3)	1.0 (0.0, 3.6)
Time between first and second surgery, mo	
Mean (SD)	25.7 (20.4)
Median (Q1, Q3)	18.4 (11.0, 33.6)
Near-term repeat surgery,[a] No. (%)	1601 (49.1)
Patients with ≥3 surgeries	656 (1.9)
Time between index and first surgery, mo	
Mean (SD)	4.3 (9.0)
Median (Q1, Q3)	0.9 (0.0, 3.7)
Time between first and second surgery, mo	
Mean (SD)	21.0 (15.0)
Median (Q1, Q3)	16.2 (11.2, 26.1)
Time between second and third surgery, mo	
Mean (SD)	21.1 (15.9)
Median (Q1, Q3)	16.0 (10.7, 25.3)
Near-term repeat surgery,[a] No. (%)	319 (48.6)
Patients with ≥4 surgeries	197 (0.6)
Time between index and first surgery, mo	
Mean (SD)	3.9 (8.8)
Median (Q1, Q3)	0.8 (0.0, 3.5)
Time between first and second surgery, mo	
Mean (SD)	18.2 (10.9)
Median (Q1, Q3)	15.3 (10.8, 21.0)
Time between second and third surgery, mo	
Mean (SD)	18.6 (14.8)
Median (Q1, Q3)	14.0 (9.3, 21.2)
Time between third and fourth surgery, mo	
Mean (SD)	19.5 (13.2)
Median (Q1, Q3)	15.3 (10.5, 24.3)
Near-term repeat surgery,[a] No. (%)	74 (37.6)

Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyps; NP, nasal polyp; Q, quartile.

[a]Surgeries within 180 days of the previous surgery were counted as near-term repeat surgeries and were not included as subsequent (ie, second or third) surgeries. Near-term repeat surgeries were identified with the same codes used to identify NP surgeries. Multiple NP surgeries on the same day were not counted as near-term repeat surgeries.

require surgery. Thus, blood eosinophil count and comorbid asthma may be useful markers for endophenotyping patients with CRSwNP. A better understanding of this ''severe'' patient endophenotype and the underlying drivers of disease will allow for an improved and more personalized treatment approach, potentially including closer outpatient follow-up, shared decision-making with healthcare professionals, cospecialty management, and tailored biologic treatments for CRSwNP.

Author Contributions

Victoria S. Benson, contributed to the conception or design of the study, the acquisition of data, and to data analysis or interpretation, contributed to the development of the manuscript, drafted the work or revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work; **Guillaume Germain**, contributed to the conception or design of the study, the acquisition of data, and to data analysis or interpretation, contributed to the development of the manuscript, drafted the work or revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work; **Robert H. Chan**, contributed to the conception or design of the study and to data analysis or interpretation, contributed to the development of the manuscript, drafted the work or revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work; **Ana R. Sousa**, contributed to the conception or design of the study and to data analysis or interpretation, contributed to the development of the manuscript, drafted the work or revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work; **Shibing Yang**, contributed to the conception or design of the study and to data analysis or interpretation, contributed to the development of the manuscript, drafted the work or revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work; **Jared Silver**, contributed to the conception or design of the study and to data analysis or interpretation, contributed to the development of the manuscript, drafted the work or revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work; **Mei Sheng Duh**, contributed to the conception or design of the study and to data analysis or interpretation, contributed to the development of the manuscript, drafted the work or revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work; **Rose Chang**, contributed to the conception or design of the study and to data analysis or interpretation, contributed to the development of the manuscript, drafted the work or revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work; **François Laliberté** contributed to the conception or design of the study, and to data analysis or interpretation, contributed to the development of the manuscript, drafted the work or revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work; **Joseph K. Han** contributed to data analysis or interpretation and contributed to the development of the manuscript, drafted the work or revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Disclosures

Competing interests: VSB, RHC, ARS, and JS are employees of GSK and own stocks/shares in GSK. SY was an employee of GSK at the time of this study and owns stocks/shares in GSK. GG,

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Supplemental Material

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