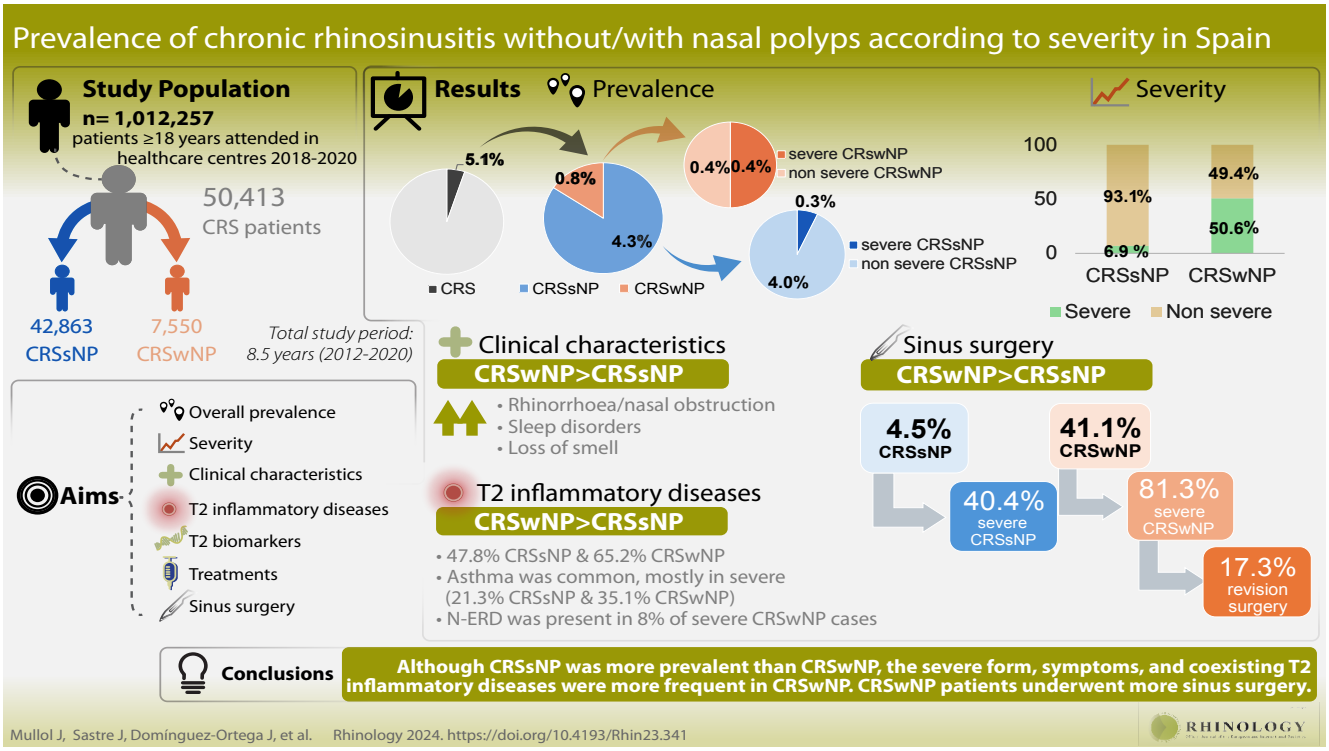
# Prevalence of chronic rhinosinusitis without/with nasal polyps according to severity in Spain

Joaquim Mullol[1], Joaquín Sastre[2], Javier Domínguez-Ortega[3], Marina Blanco-Aparicio[4], José Antonio Castillo Vizuete[5], Isam Alobid[6], Montse García-Vitoria[7], Paloma I. Palomo-Jiménez[8]

**Rhinology 62: 4,** 421 - 431, 2024
https://doi.org/10.4193/Rhin23.341




## Abstract

**Background**: The worldwide prevalence range of chronic rhinosinusitis (CRS) is 5-12%; from this, 20 % have nasal polyps. Due to the little epidemiological data about CRS in the Spanish population, this study analyses the prevalence and severity of CRS with (CRSwNP) or without (CRSsNP) nasal polyps, and their connection with other coexisting type 2 inflammatory diseases in Spain. **Methodology**: This is a retrospective, large-scale, nationwide, epidemiological study based on the electronic medical records from the BIG-PAC® database. Patients diagnosed of CRSsNP and CRSwNP were identified using specific disease codes. The severe form of the disease was defined as patients who received at least a long course of antibiotics in CRSsNP or ≥2 short courses of systemic corticosteroids in CRSwNP in ≤12 months during the last 2 years, and/or had previous sinus surgery. Physician-diagnosed prevalence, sociodemographic and clinical characteristics, and disease severity were assessed. **Results**: Out of a cohort of 1,012,257 patients (≥18 years old), 42,863 and 7,550 patients with diagnosed CRSsNP and CRSwNP, respectively, were analysed. The overall prevalence of diagnosed CRS was 5.1%, being 4.3% and 0.8% for CRSsNP and CRSwNP, respectively. Patients with CRSwNP and severe forms of the disease were older and had higher levels of type 2 inflammatory biomarkers than CRSsNP patients and non-severe disease. **Conclusions**: Although CRSsNP was more prevalent than CRSwNP, the severe forms of CRS were more frequent in patients with CRSwNP. In addition, CRSwNP patients had a higher incidence of coexisting type 2 inflammatory diseases.

**Key words**: chronic rhinosinusitis, nasal polyps, comorbidity, prevalence, type-2 inflammation

## Introduction

Rhinosinusitis is an inflammatory disease of the nose and paranasal sinuses mucosa [1]. It is defined as the presence of nasal congestion/obstruction and/or anterior/posterior rhinorrhoea, associated with facial pain/pressure and/or partial/total loss of smell (LoS) [1,2]. If symptoms last ≥12 weeks, it is considered chronic rhinosinusitis (CRS) [1,3], whose prevalence ranges between 5% and 12% in the general population worldwide [4].

CRS is a multifactorial inflammatory disease, with two main distinguishable phenotypes, CRS without (CRSsNP) or with (CRSwNP) nasal polyps (NP) [1,2]. CRSsNP, characterised by fibrosis, basement membrane thickening and goblet cell hyperplasia, affects around 80% of CRS cases [5,6]. CRSwNP patients have bilateral development of benign oedematous NP from the ethmoid sinuses into the nasal cavity [1,3]. Type 2 (T2) inflammation plays a main underlying role in CRS, predominantly in patients with CRSwNP [1,2,7]. In fact, CRS is frequently associated with other T2 inflammatory diseases in the upper and lower respiratory tract (allergic rhinitis [AR], asthma, aspirin/non-steroidal anti-inflammatory drug [NSAID]-exacerbated respiratory disease [N-ERD], atopic dermatitis [AD], or eosinophilic esophagitis) [1,3,8]. Up to 67%, and around 10-30%, of patients with CRSwNP have comorbid asthma or N-ERD, respectively [3,9]. Due to its symptoms and comorbidities, CRS causes a significant impact on patients' quality of life (QoL) [10], similar to that of chronic obstructive pulmonary disease, asthma, or diabetes [11].

The appropriate medical treatment for CRS is based on saline nasal irrigations and intranasal corticosteroids (INCS) [1,12]. CRSsNP patients may also be treated with short cycles of systemic corticosteroids (SCS), and/or short-term course of antibiotics in disease exacerbation [12]. Short-term SCS are advised in CRSwNP [1, 12-14]. When medication fails to control CRS, endoscopic sinus surgery (ESS) is recommended [1, 12]. Recurrence rates of ESS in CRSwNP patients range between 25-79% at long term (5 to 12 years) [15-17]. A study conducted in a tertiary referral centre reported that ≥40% of CRS patients who had previously had ESS, remained uncontrolled 3-5 years after ESS, with sinonasal symptoms (blocked nose, LoS, and sleep disturbance) [18], which may worsen patients' QoL [11,19].

There is a lack of epidemiological studies focused on CRSsNP, and few extensive epidemiological studies on CRSwNP, performed in the Spanish population. This is the first study analysing CRSsNP and CRSwNP prevalence and severity, and their association with other coexisting T2 inflammatory diseases in Spain.

## Materials and methods

### Design

This retrospective, observational, cross-sectional study, based on electronic medical records (EMRs) from the BIG-PAC® database, collected information from 1.8 million individuals (representative of the Spanish population, according to an internal study comparing the Spanish age pyramid in 2018 and the population data from BIG-PAC®) [20, 21]. EMRs contained in BIG-PAC® come from publicly-owned services (primary care and hospital) data of integrated health areas from seven different Spanish regions and includes hospital medication, and procedures. EMRs undergo a rigorous anonymization process in the source centres in compliance with data protection regulations [22].

This 8.5-year study started on 01/01/2012 and ended on the index date (30/06/2020). The study covered two main periods: a previous 6.5-year period (from 01/01/2012 to 30/06/2018) and a 2-year retrospective period (from 01/07/2018 to 30/06/2020). Prevalence was calculated on the 01/07/2018; medications were collected in the retrospective period. Data on clinical outcomes, on coexisting T2 inflammatory diseases of patients, and T2 biomarkers were taken on the index date. Lastly, surgery records were gathered from 01/01/2012 to 30/06/2020.

### Study population

Patients with diagnosis of CRS prior to 01/07/2018 were selected from BIG-PAC® database and classified by physician diagnosis into CRSsNP or CRSwNP cohorts. The CRSsNP cohort included patients with a CRS diagnosis code who did not have a NP code. Patients with a NP diagnosis code (with or without a CRS code) were included in the CRSwNP cohort (Figure 1). Diagnoses were defined according to the International Classification of Diseases, 9th edition, Clinical Modification [23]. Inclusion and exclusion criteria are detailed in Table S1.

In the index date (30/06/2020), patients were classified according to severity as defined in the EPOS 2012 and confirmed by EPOS 2020 guidelines [1, 24]. Similarly to Sánchez Collado et al. [25], a two-year retrospective period was considered for severity classification according to medication data; surgeries were regarded for the last 8.5 years. Therefore, patients with CRSsNP were classified as severe when undergoing a) long course of antibiotics (≥1 month) in ≤12 months during the 2-year retrospective period; and/or b) sinonasal surgery during the total study period. Patients with CRSwNP were classified as severe when undergoing a) ≥2 short courses of SCS (≥5 days) in ≤12 months, during the 2-year retrospective period; and/or b) sinonasal surgery during the total study period (8.5-year period) (details in Table S2). To avoid selection bias, medication used for severity classification were those prescribed linked to a CRS code.

### Outcomes

*Overall prevalence*

Overall prevalence (the prevalence of a disease measured at a particular time) [26] was determined as the total number of diagnosed CRS (CRSsNP or CRSwNP) cases in the database (≥18 years) on 01/07/2018 divided by the total number of active patients on the database on the 01/07/2018 (1,012,257 patients). It was expressed as the frequency of the prevalence per

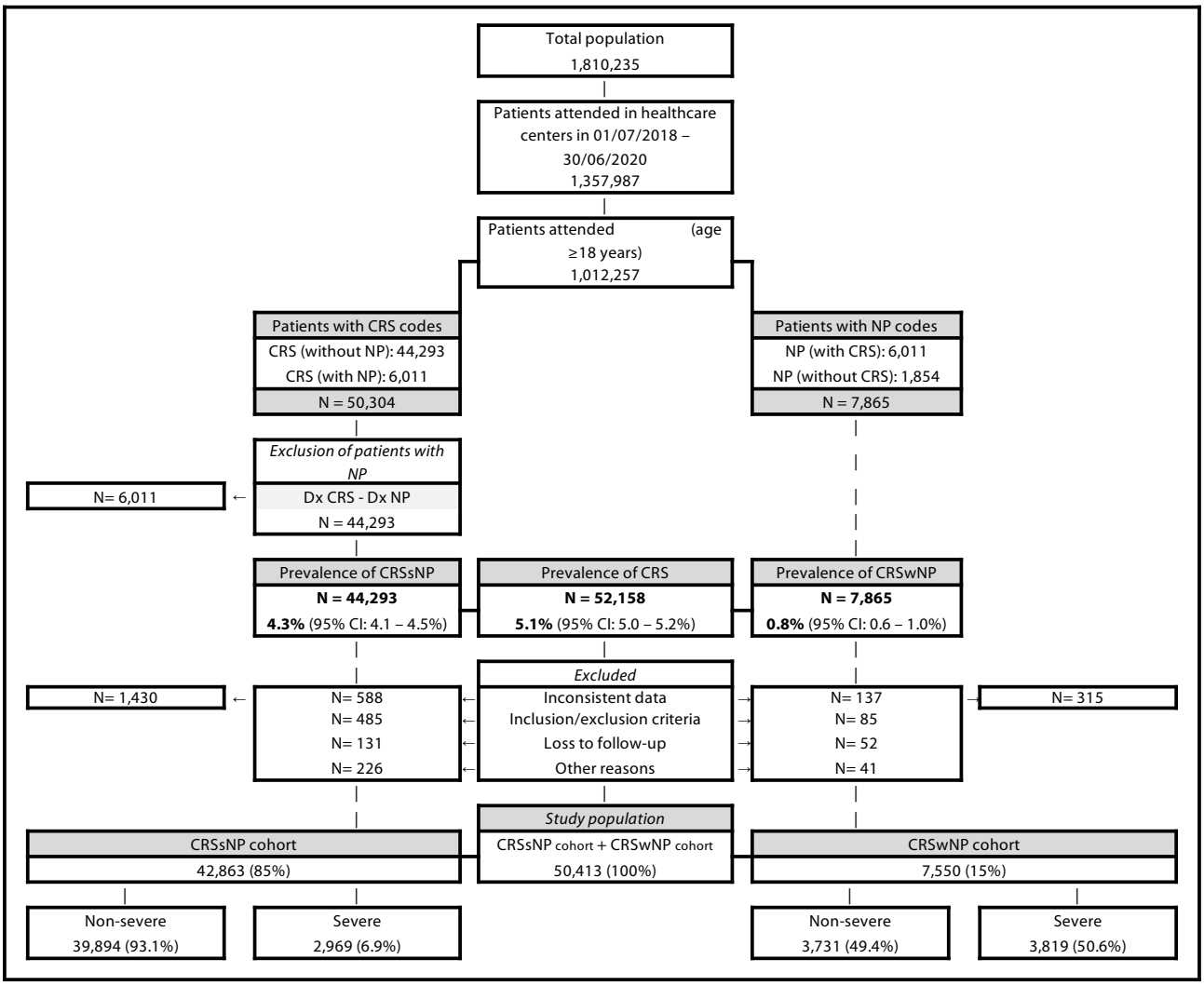



Figure 1. Flowchart of the chronic rhinosinusitis study population. The study cohorts were obtained according to the diagnostic coding of patients: the final count was N= 42,863 (CRSsNP) and N= 7,550 (CRSwNP) patients. Patients with CRSwNP were obtained directly from the database, without any specific CRS code with the assumption that patients with CRSwNP also had CRS. 23.6% of patients (N=1,854) with NP codes had no previous diagnosis of CRS; whereas these patients in the CRS cohort were excluded (N=6,011; 11.9%). Abbreviations: CI, confidence interval; CRS: chronic rhinosinusitis; CRSsNP: CRS without nasal polyps; CRSwNP: CRS without nasal polyps; Dx: diagnosis; NP: nasal polyps.

one hundred patients. Due to the similarity between the study population and the Spanish population in terms of age and sex, no standardization of results was necessary [20].

*Demographic outcomes and comorbidities*

Demographic variables were measured on the index date and included age, sex, body mass index (BMI) and time to diagnosis. Comorbidities and T2 inflammatory diseases were also indicated (Table S3). Severe asthma was defined according to the Spanish Guidelines for the Management of Asthma (GEMA 5.3; steps 5-6) [27] and based on that, a group of experts defined patient severity as patients treated with: a) high-dose inhaled corticosteroids-LABA (>6 months during past year; or >12 months during past two years); b) SCS (>6 months during the past year or >12 months during the past two years); and/or c) biologic therapy during the past two years. Patients with severe AD were defined as those treated with a) immunosuppressants; b) biologic therapy; and/or c) having a hospital admission for AD; during the last two years. This definition was based on the European guidelines of AD [28]. Medications used to classify severity in patients with asthma and DA were linked to the diagnosis codes.

Serum total immunoglobulin E (IgE) and blood eosinophils counts (BEC) were determined on the index date. Sinonasal symptoms, such as rhinorrhoea, nasal obstruction, LoS, and sleep disorders were also recorded.

*Pharmacological and surgical treatment*

Medicines prescribed linked to a CRS code were identified with

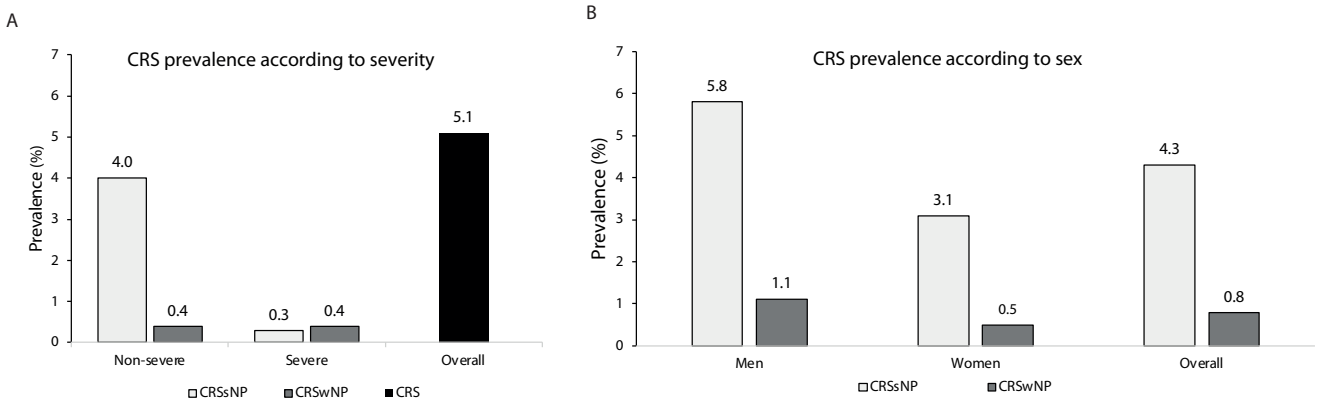



Figure 2. Prevalence of CRS, CRSsNP, and CRSwNP phenotypes according to severity and sex. Columns represent the estimated percentage of patients with the corresponding diagnosis in the population of patients attended and registered in the database on 30/06/2020. Results are expressed as mean values and 95% confidence intervals. Abbreviations: CI: confidence interval; CRS: chronic rhinosinusitis; CRSsNP: chronic rhinosinusitis without nasal polyps; CRSwNP: chronic rhinosinusitis with nasal polyps. Statistical analysis: *, p<0.05.

the ATC Classification System [29]: systemic antibiotics, INCS, SCS, leukotriene receptor antagonists (LTRA), and antihistamines. The number and duration of SCS cycles were assessed. Pharmacological therapies were analysed during the retrospective period (2-year retrospective period), whereas sinonasal surgeries were recorded during the total study period (8.5-year full study period).

### Statistical analysis

Search criteria were based on computer sentences (SQL script). Data were carefully reviewed through exploratory analysis, looking for recording or coding errors. Data validation was performed to ensure the quality of the results. Descriptive-univariate statistical analysis was conducted. Data values were given as mean (standard deviation, SD), median (interquartile range) or percentage. For bivariate analysis (comparison between non-severe vs. severe CRSsNP or CRSwNP and CRSsNP vs. CRSwNP), Wilcoxon rank sum test and Pearson's Chi-squared tests for independent groups were performed. SPSSWIN statistical software v.23 was used, establishing a statistical significance of p<0.05.

## Results

### Study population

Out of 1,012,257 patients ≥18 years old in the database, 50,304 patients diagnosed with CRS codes (with or without NP codes) and 7,865 patients diagnosed with NP codes (with or without CRS codes) were selected. Patients with NP codes (6,011) were excluded from the CRSsNP group. Finally, 50,413 patients met inclusion/exclusion criteria (42,863 in the CRSsNP cohort and 7,550 in the CRSwNP cohort) on the 01/07/2018-30/06/2020 and were divided into severity subgroups: a) non-severe (N=39,894; 93.1%) vs. severe (N=2,969; 6.9%) CRSsNP; and b) non-severe (N=3,731; 49.4%) vs. severe (N=3,819; 50.6%) CRSwNP (Figure 1).

### Prevalence

The overall prevalence of diagnosed CRS in adults was 5.1% (95% confidence interval, 95% CI; 5.0%-5.2%) diagnosed CRSsNP and CRSwNP prevalence rates were 4.3% (95% CI; 4.1%-4.5%) and 0.8% (95% CI; 0.6%-1.0%) (Figure 1), of which 0.3% and 0.4% were severe, respectively (Figure 2A). Prevalence was significantly higher for males than females in both groups (p=0.005) (Figure 2B).

### Demographic characteristics

CRS patients had a mean age of 43.9 years (61.7% men). CRSsNP patients were younger than CRSwNP, particularly those with non-severe disease; mean (SD) time from diagnosis was 5.2 (1.8) and 10.0 (2.3) years, respectively. Their mean (SD) BMI was 27.3 (3.9) and 28.6 (3.9) kg/m$^2$. Demographic characteristics are detailed in Table 1.

### Patient-reported outcomes

Overall sinonasal symptoms. CRSwNP patients had more symptoms (rhinorrhoea/nasal obstruction [p<0.001], sleep disorders [p<0.001], and LoS [p<0.001]) than CRSsNP patients; these were more frequent in severe than in non-severe patients (p<0.001 for all comparisons) (Table 1).

Coexisting T2 inflammatory diseases. Half of the CRS population had other coexisting T2 diseases (50.4%); frequency was higher in CRSwNP than CRSsNP patients (65.2% vs. 47.8%) (Table 2). This was more obvious in severe patients, who followed the same trend between CRSwNP and CRSsNP (70.6% and 51.8% patients, respectively, suffered from other T2 inflammatory condition). Patients with CRSwNP, regardless of their severity status, showed higher frequency of AR, AD, asthma, and N-ERD compared to CRSsNP patients (p<0.001); this difference in phenotypes was more striking in severe patients (AR 25.4% vs. 42.2%, asthma 21.3% vs. 35.5%, AD 17.0% vs. 25.0% and N-ERD

Table 1. Baseline characteristics of patients with CRSsNP and CRSwNP according to severity.

| Study outcomes | Total | CRSsNP | | | | CRSwNP | | | | p (CRSsNP vs. CRSwNP) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Total | Non-severe | Severe | p (non-severe vs. severe) | Total | Non-severe | Severe | p (non-severe vs. severe) | |
| Number of patients, N (%) | 50,413 (100) | 42,863 (100) | 39,894 (93.1) | 2,969 (6.9) | | 7,550 (100) | 3,731 (49.4) | 3,819 (50.6) | | |
| **Demographic characteristics** | | | | | | | | | | |
| Age, years, mean (SD) | 43.9 (15.3) | 42.8 (15.0) | 42.7 (15.1) | 44.1 (12.8) | **<0.001** | 50.1 (15.5) | 48.2 (15.3) | 51.9 (15.5) | **<0.001** | **<0.001** |
| Age ranges in years, N (%) | | | | | | | | | | |
| 18 - 44 | 28,953 (57.4) | 25,901 (60.4) | 24,341 (61) | 1,560 (52.5) | | 3,052 (40.4) | 1,703 (45.6) | 1,349 (35.3) | | |
| 45 – 64 | 16,073 (31.9) | 12,975 (30.3) | 11,729 (29.4) | 1,246 (42) | | 3,098 (41.0) | 1,437 (38.5) | 1,661 (43.5) | | |
| 65 - 74 | 3,711 (7.4) | 2,841 (6.6) | 2,706 (6.8) | 135 (4.5) | **<0.001** | 870 (11.5) | 389 (10.4) | 481 (12.6) | **<0.001** | **<0.001** |
| ≥ 75 | 1,676 (3.3) | 1,146 (2.7) | 1,118 (2.8) | 28 (0.9) | | 530 (7.0) | 202 (5.4) | 328 (8.6) ‡ | | |
| Sex, male, N (%) | 31,096 (61.7) | 26,250 (61.2) | 24,410 (61.2) | 1,840 (62.0) | | 4,846 (64.2) | 2,383 (63.9) | 2,463 (64.5) | 0.572 | <0.001 |
| Active smoking, N (%) | 7,602 (15.1) | 6,606 (15.4) | 6,134 (15.4) | 472 (15.9) | | 996 (13.2) | 469 (12.6) | 527 (13.8) | 0.115 | <0.001 |
| **Systemic comorbidities** | | | | | | | | | | |
| Nº of comorbidities, mean (SD) | 1.2 (1.1) | 1.2 (1.0) | 1.2 (1.0) | 1.2 (1.0) | **<0.001** | 1.6 (1.3) | 1.5 (1.2) | 1.8 (1.3) | **<0.001** | **<0.001** |
| Arterial hypertension, N (%) | 8,067 (16.0) | 6,689 (15.6) | 6,186 (15.5) | 503 (16.9) | **0.038** | 1,378 (18.3) | 632 (16.9) | 746 (19.5) | **0.004** | **<0.001** |
| Diabetes mellitus, N (%) | 3,062 (6.1) | 2,351 (5.5) | 2,178 (5.5) | 173 (5.8) | 0.396 | 711 (9.4) | 307 (8.2) | 404 (10.6) | **<0.001** | **<0.001** |
| Heart/renal failure, N (%) | 873 (1.7) | 705 (1.6) | 653 (1.6) | 52 (1.8) | 0.636 | 168 (2.2) | 71 (1.9) | 97 (2.5) | **0.061** | **<0.001** |
| Cardiovascular events, N (%) | 2,915 (5.8) | 2,416 (5.6) | 2,227 (5.6) | 189 (6.4) | **0.074** | 499 (6.6) | 234 (6.3) | 265 (6.9) | 0.243 | **0.001** |
| Parkinson's disease, N (%) | 110 (0.2) | 35 (0.1) | 25 (0.1) | 10 (0.3) | **<0.001** | 75 (1.0) | 38 (1.0) | 37 (1.1) | 0.828 | **<0.001** |
| Dementia, N (%) | 260 (0.3) | 156 (0.2) | 152 (0.1) | 4 (0.2) | **0.032** | 104 (1.4) | 31 (0.8) | 73 (1.9) | **<0.001** | **<0.001** |
| **Specific symptoms, N (%)** | | | | | | | | | | |
| Rhinorrhoea / nasal obstruction | 41,603 (82.5) | 35,075 (81.8) | 32,539 (81.6) | 2,536 (85.4) | **<0.001** | 6,528 (86.5) | 3,175 (85.1) | 3,353 (87.8) | **<0.001** | **<0.001** |
| Loss of smell | 9,252 (18.4) | 6,452 (15.1) | 5,839 (14.6) | 613 (20.6) | **<0.001** | 2,800 (37.1) | 1,133 (30.4) | 1,667 (43.7) | **<0.001** | **<0.001** |
| Sleep disorders | 10,560 (20.9) | 7,727 (18.0) | 7,051 (17.7) | 676 (22.8) | **<0.001** | 2,833 (37.5) | 1,286 (34.5) | 1,547 (40.5) | **<0.001** | **<0.001** |
| **Other outcomes** | | | | | | | | | | |
| Time from diagnosis, mean (SD) years | 6 (2.5) | 5.2 (1.8) | 5.2 (1.8) | 6 (1.8) | **<0.001** | 10.0 (2.3) | 9 (2.2) | 10.9 (1.9) | **<0.001** | **<0.001** |
| BMI, kg/m$^2$, mean (SD) | 27.2 (3.9) | 27.3 (3.9) | 26.9 (3.9) | 27.7 (4.2) | **<0.001** | 28.6 (3.9) | 28.5 (3.8) | 28.6 (4) | **0.001** | **<0.001** |

Values expressed as percentage (%) or mean (SD: standard deviation) or median (percentile 25 – percentile 75), p: statistical significance. Dementia includes all types of dementia, like Alzheimer's disease. Abbreviations: BMI: body mass index, kg/m2. P: percentiles. CRSsNP: chronic rhinosinusitis without nasal polyps; CRSwNP: chronic rhinosinusitis with nasal polyps.

3.6% vs. 8.0%) (Table 2).

### T2 inflammation biomarkers

BEC. CRSwNP patients had higher BEC than CRSsNP (271.9 vs. 208.6 cells/µL, p<0.001). Severe patients had higher BEC than non-severe for both CRSsNP (227.3 vs. 207.2 cells/µL; p<0.001) and CRSwNP (292.6 vs. 250.2 cells/µL; p<0.001) (Table 2).
Total serum IgE. Levels were higher in CRSwNP than in CRSsNP (116.7 vs. 93.4 kU/L, p<0.001), and in severe than in non-severe CRS (both p<0.001) (Table 2).

### Medications

Overall, 42.3% and 9.0% of patients used INCS and SCS, respectively; their use was higher in CRSwNP than in CRSsNP patients (p<0.001). Patients with severe CRS used more INCS and SCS than those non-severe (p<0.003, all comparisons). In addition, CRSwNP patients needed twice as many SCS cycles compared to CRSsNP patients (2.5 vs. 1.2, p<0.001), considering that 48.3% of severe CRSwNP patients did not receive treatment with SCS during the retrospective period (Table 3). CRSwNP patients were prescribed more medications than CRSsNP (3 vs. 2, p<0.001), particularly those with severe disease (p<0.001). Overall, CRSwNP patients (and especially severe patients) used more antibiotics, LTRA, and antihistamines (p<0.001, all comparisons) (Table 3).

### Sinus surgery in severe patients

In the 8.5-years total study period, CRSsNP severe patients who underwent surgery accounted for 4.5% of the overall CRSsNP population (40.4% in severe patients), while, in the case of CRSwNP patients, 41.1% had sinus surgery (81.3% in severe patients, 17.3% of which required revision surgery). ESS was the most frequent surgical approach (Table 4).

## Discussion

To our knowledge, this is the first study in Spain to gather

Table 2. Coexisting Type 2 inflammatory diseases of patients and T2 biomarkers (eosinophils and immunoglobulin E levels in blood) with CRSsNP and CRSwNP according to severity at index date.

| Study outcomes | Total | CRSsNP | | | | CRSwNP | | | | p (CRSsNP vs. CRSwNP) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Total | Non-severe | Severe | p (non-severe vs. severe) | Total | Non-severe | Severe | p (non-severe vs. severe) | |
| Number of patients, N (%) | 50,413 (100) | 42,863 (100) | 39,894 (93.1) | 2,969 (6.9) | | 7,550 (100) | 3,731 (49.4) | 3,819 (50.6) | | |
| Coexisting Type 2 inflammatory diseases, mean (SD) | 0.6 (0.8) | 0.6 (0.7) | 0.6 (0.7) | 0.7 (0.8) | **<0.001** | 1.0 (0.9) | 0.9 (0.9) | 1.1 (0.9) | **<0.001** | **<0.001** |
| Coexisting Type 2 inflammatory diseases, N (%) | 25,391 (50.4) | 20,472 (47.8) | 18,934 (47.5) | 1,538 (51.8) | **<0.001** | 4,919 (65.2) | 2,224 (59.6) | 2,695 (70.6) | **<0.001** | **<0.001** |
| Allergic rhinitis (total) | 13,428 (26.6) | 10,638 (24.8) | 9,883 (24.8) | 755 (25.4) | 0.424 | 2,790 (37.0) | 1,179 (31.6) | 1,611 (42.2) | **<0.001** | **<0.001** |
| Asthma (total) | 9,873 (19.6) | 7,481 (17.5) | 6,850 (17.2) | 631 (21.3) | **<0.001** | 2,392 (31.7) | 1,053 (28.2) | 1,339 (35.1) | **<0.001** | **<0.001** |
| Severe asthma | 2,324 (4.6) | 1,607 (3.7) | 1,425 (3.6) | 182 (6.1) | **<0.001** | 717 (9.5) | 313 (8.4) | 404 (10.6) | **0.001** | **<0.001** |
| Atopic dermatitis (total) | 8,351 (16.6) | 6,591 (15.4) | 6,087 (15.3) | 504 (17.0) | **0.012** | 1,760 (23.3) | 807 (21.6) | 953 (25.0) | **0.001** | **<0.001** |
| Severe atopic dermatitis | 3,155 (6.2) | 2,448 (5.7) | 2,234 (5.6) | 214 (7.2) | **<0.001** | 707 (9.4) | 304 (8.1) | 403 (10.5) | **<0.001** | **<0.001** |
| N-ERD | 1,240 (2.5) | 738 (1.7) | 630 (1.6) | 108 (3.6) | **<0.001** | 502 (6.6) | 195 (5.2) | 307 (8.0) | **<0.001** | **<0.001** |
| Patients with available blood eosinophil count, N (%) | 50,413 (100) | 42,863 (100) | 39,894 (100) | 2,969 (100) | | 7,550 (100) | 3,731 (100) | 3,819 (100) | | |
| Eosinophil counts, cells/µL, mean (SD) | 217 (199.2) | 208.6 (196.2) | 207.2 (196.9) | 227.3 (187) | **<0.001** | 271.9 (207.1) | 250.2 (195.6) | 292.6 (215.6) | **<0.001** | **<0.001** |
| Patients with available serum total IgE values, N (%) | 28,763 (57.1) | 21,984 (51.3) | 19,825 (49.7) | 2,159 (72.7) | | 6,779 (89.8) | 3,267 (87.6) | 3,512 (92.0) | | |
| Total IgE levels, kU/L, mean (SD) | 96.9 (87.2) | 93.4 (77.8) | 92.9 (78.0) | 99.9 (74.2) | **<0.001** | 116.7 (82.5) | 109.2 (77.8) | 124.2 (86.3) | **<0.001** | **<0.001** |

Values expressed as percentage (%) or mean (SD: standard deviation) or median (percentile 25 – percentile 75), p: statistical significance. N-ERD (NSAID-exacerbated respiratory disease) was defined as the presence of codes regarding CRS, asthma, and intolerance to NSAID (Non-Steroidal Anti-Inflammatory Drug). Type 2 inflammatory diseases include asthma, atopic dermatitis, allergic rhinitis, NSAID intolerance and N-ERD; Abbreviations: CRSsNP: chronic rhinosinusitis without nasal polyps; CRSwNP: chronic rhinosinusitis with nasal polyps, IgE: immunoglobulin E, N-ERD: non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease.

national data on CRS prevalence, and to analyse it according to severity criteria. In our study, the prevalence of CRS was 5.1%, CRSsNP was more prevalent than CRSwNP (4.3% vs. 0.8%). Severe CRS was more frequent in CRSwNP than in CRSsNP patients (50.6% vs. 6.9%). In comparison with CRSsNP, CRSwNP patients were older and had higher levels of T2 inflammatory biomarkers and coexisting T2 inflammatory diseases. Not surprisingly, CRSwNP patients usually suffered from more specific respiratory symptoms (obstruction/rhinorrhoea, LoS, sleep disorder) than CRSsNP patients, particularly those with severe disease.

The epidemiology of CRS has been previously studied in several countries worldwide. The overall prevalence of symptom-based CRS varies between 5.5% and 28% [1, 30]. The prevalence of CRS was reportedly 11%, 12%, and 10.8% in Europe [30], the United States [31] and Korea [32], respectively, although, in line with our data, a lower prevalence (4-7%) was estimated in Canada [33], Brazil [34], China [35], and Denmark [12]. In addition, a study in the Netherlands estimated that the prevalence of CRS ranged between 3.0% and 6.4% depending on the Lund-Mackay scoring system [4]. It needs to be considered the time when these overall prevalences were calculated, and that the selection of patients or their definition/diagnostic criteria of CRS may impact the result of the study.

Regarding phenotypes, a study developed in the United States recorded 4,535 patients with CRSsNP (82%) and 990 with CRSwNP (18%), leading to a 4:1 ratio, aligned with the proportion showed in our study in the Spanish population (5.6:1) [36]. A systematic review reported that the prevalence rate of CRSwNP in the general population ranged between 1% and 2.6% [37]. The overall prevalence of diagnosed CRSwNP in our study seemed to be lower than that previously published in population-based studies. However, our results are aligned with other Spanish studies that reported a 0.16% and 0.49% prevalence [25, 38]. The results of the Spanish studies are consistent with recent published prevalence in other countries as Poland (0.52%) [39] or Germany (5-year prevalence: 0.58%) [40]. Disparities between studies may be associated to differences in the study period, the diagnosis criteria, the setting where patients were recorded (primary care centres, hospitals and/or emergency care facilities) and the scope of the study (regional vs. national level).

Severity was more frequent in CRSwNP than CRSsNP patients (50.6% vs. 6.9%), similarly to what has been previously published [1]. However, a Spanish regional analysis reported that 24% of

Table 3. Medical treatments prescribed according to CRS severity in the retrospective period (2018-20).

| Study outcomes | Total | CRSsNP | | | | CRSwNP | | | | p (CRSsNP vs. CRSwNP) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Total | Non-severe | Severe | p (non-severe vs. severe) | Total | Non-severe | Severe | p (non-severe vs. severe) | |
| Number of patients, N (%) | 50,413 (100) | 42,863 (100) | 39,894 (93.1) | 2,969 (6.9) | | 7,550 (100) | 3,731 (49.4) | 3,819 (50.6) | | |
| **Corticosteroids** | | | | | | | | | | |
| Intranasal corticosteroids, N patients (%) | 21,325 (42.3) | 14,659 (34.2) | 12,966 (32.5) | 1,692 (57.0) | **<0.001** | 6,667 (88.3) | 3,112 (83.4) | 3,552 (93.0) | **<0.001** | **<0.001** |
| Daily dose in µg, mean (SD) | 119.3 (164.1) | 99.6 (142.7) | 97.1 (146.5) | 110.1 (125.7) | **0.002** | 186 (208.6) | 142.8 (262.7) | 205 (176.8) | **<0.001** | **<0.001** |
| SCS N patients (%) | 4,526 (9.0) | 2,029 (4.7) | 1,693 (4.2) | 336 (11.3) | **<0.001** | 2,497 (33.1) | 523 (14.0) | 1,974 (51.7) | **<0.001** | **<0.001** |
| Number of SCS cycles, mean (SD) | 1.9 (1.0) | 1.2 (0.5) | 1.1 (0.5) | 1.3 (1.3) | **<0.001** | 2.5 (0.9) | 1 (0.0) | 2.9 (2.9) | **<0.001** | **<0.001** |
| **Number of SCS cycles (≥5days) within one year, N patients (%)** | | | | | | | | | | |
| 0 cycles | 43,331 (86.0) | 40,834 (95.3) | 38,201 (95.8) | 2,633 (88.7) | | 5,053 (66.9) | 3,208 (86.0) | 1,845 (48.3) | | |
| 1 cycle | 2,443 (4.9) | 1,813 (4.2) | 1,528 (3.8) | 285 (9.6) | | 630 (8.3) | 523 (14.0) | 107 (2.8) | | |
| 2 cycles | 337 (0.7) | 137 (0.3) | 114 (0.3) | 23 (0.8) | **<0.001** | 200 (2.7) | 0 (0) | 200 (5.2) | **<0.001** | **<0.001** |
| 3 cycles | 1,612 (3.2) | 63 (0.2) | 40 (0.1) | 23 (0.8) | | 1,549 (20.5) | 0 (0) | 1,549 (40.6) | | |
| ≥4 cycles | 134 (0.3) | 16 (0.0) | 11 (0.0) | 5 (0.2) | | 118 (1.6) | 0 (0) | 118 (3.1) | | |
| **Other medications, N patients (%)** | | | | | | | | | | |
| Antibiotics | 19,207 (38.1) | 14,745 (34.4) | 12,048 (30.2) | 2,705 (91.1) | **<0.001** | 4,462 (59.1) | 1,955 (52.4) | 2,504 (65.6) | **<0.001** | **<0.001** |
| Antibiotics (long cycles) | 6,683 (13.3) | 2,654 (6.2) | 0 (0) | 2,654 (89.4) | - | 4,029 (53.4) | 1,745 (46.8) | 2,284 (59.8) | **<0.001** | **<0.001** |
| Antileukotrienes | 3,327 (6.6) | 2,486 (5.8) | 2,234 (5.6) | 255 (8.6) | **<0.001** | 831 (11.0) | 336 (9.0) | 496 (13.0) | **<0.001** | **<0.001** |
| Antihistamines | 19,762 (39.2) | 15,859 (37.0) | 14,601 (36.6) | 1,235 (41.6) | **<0.001** | 3,911 (51.8) | 1,675 (44.9) | 2,230 (58.4) | **<0.001** | **<0.001** |
| **Number of medications used, mean (SD)** | 2 (1.3) | 2 (1.3) | 2 (1.3) | 3 (1.3) | **<0.001** | 3 (1.4) | 2 (1.3) | 3 (1.4) | **<0.001** | **<0.001** |
| None | 8,318 (16.5) | 7,973 (18.6) | 7,221 (18.1) | 644 (21.7) | | 362 (4.8) | 254 (6.8) | 107 (2.8) | | |
| 1 | 12,150 (24.1) | 10,844 (25.3) | 10,612 (26.6) | 240 (8.1) | **<0.001** | 1,306 (17.3) | 798 (21.4) | 504 (13.2) | **<0.001** | **<0.001** |
| ≥2 | 29,945 (59.4) | 24,046 (56.1) | 22,061 (55.3) | 2,084 (70.2) | | 5,881 (77.9) | 2,679 (71.8) | 3,208 (84.0) | | |

Values expressed as percentage or mean (SD: standard deviation), p: statistical significance. P: percentiles. Oral corticosteroid cycles followed a pattern of 5-30 days in a row, with a minimum of 15 days between cycles. Abbreviations: CRSsNP: chronic rhinosinusitis without nasal polyps; CRSwNP: chronic rhinosinusitis with nasal polyps; P: percentile; SCS: systemic corticosteroids (oral); SD: standard deviation.

patients with CRSwNP had a severe disease [25]. This difference could be due among other to the fact that the total period in which the surgeries were recorded was shorter than in our study.

Gender prevalence in CRS is still on debate [1, 7, 36, 41]. Our study showed that most CRSsNP and CRSwNP patients were male (61.2% and 64.2%, respectively), in agreement with two previous Spanish studies. The first found that 59.2% of CRSwNP patients were male [38], the second established that 58.5%-61.4% of their CRSwNP population were male in all severity levels [25].

CRS prevalence is associated with age, since CRSwNP patients develop NP in more advanced disease stages [1, 42]. Our study found differences in the mean age of both populations (42.8 and 50.1 years, p<0.001) respectively; CRSwNP developed in >45- year-olds, a late disease onset similarly to other T2 diseases. Studies differ in their CRS population mean age. Benjamin et al. found no differences in the mean age of CRSsNP/CRSwNP (50.8 years vs. 50.3 years) [36], while another study reported a median age of 38 vs. 45 years old, respectively [7]. This may be related to the smaller size of those study populations; our population was almost 10 times bigger (50,413 vs. 5,780 patients)[7, 36].

A close connection between CRS and eosinophilia has been widely reported, having eosinophilic CRS a worse prognosis [43] and a higher risk for NP recurrence [44]. Our study showed that CRSwNP patients, particularly those with severe disease, had higher BEC. Besides, we observed that CRSwNP patients, especially those with severe disease, had higher IgE levels than CRSsNP, similar to what Castillo et al. reported in asthmatic patients with CRSwNP / CRSsNP [45].

Patients with CRS, mostly with CRSwNP and severe disease, suffer of frequent sinonasal symptoms, including reduction/LoS [46-50]. Sleep problems are 50-90% more common among CRS patients [51]. Nevertheless, all these studies suggest that patients with CRSwNP have a poorer health status than patients with CRSsNP.

Table 4. Sinonasal surgeries performed in patients with severe CRSwNP and severe CRSsNP.

| Time period | Previous period | Retrospective period | Total period |
|---|---|---|---|
| **Severe CRSwNP (N= 3,819)** | | | |
| Patients with sinus surgery, N (%) | 1,894 (49.6) | 1,531 (40.1) | 3,103 (81.3) |
| Number of sinus surgeries, N (%) | | | |
| 1 surgery | 1,671 (43.8) | 1,389 (36.4) | 2,442 (63.9) |
| ≥ 2 surgeries | 223 (5.8) | 142 (3.7) | 661 (17.3) |
| Types of sinus surgery Total, N | 2,123 | 1,687 | 3,810 |
| ESS†, N (%) | 1,859 (87.8) | 1,549 (91.8%) | 3,408 (89.5) |
| Other sinonasal surgeries, N (%) | 264 (12.4) | 101 (8.2%) | 402 (10.5) |
| **Severe CRSsNP (N= 2,969)** | | | |
| Patients with surgery, N (%) | 745 (25.1) | 479 (16.1) | 1,200 (40.4) |

Previous period: 01/01/2012 - 30/06/2018 (6.5 years). Retrospective period: 01/07/2018 – 30/06/2020 (2 years). Total period: 01/01/2012 – 30/06/2020 (8.5 years). Abbreviations: CRSsNP: chronic rhinosinusitis without nasal polyps. CRSwNP: chronic rhinosinusitis with nasal polyps; ESS: endoscopic sinus surgery. Surgeries were analysed in the overall population. Having a sinonasal surgery classified the patient into the severe group according to the severity criteria.

Moreover, CRS patients commonly suffer from coexisting T2 inflammatory diseases, such as asthma, AR, N-ERD, and AD [1, 9, 37, 52-55]. Our study reported that 17.5% and 31.7% of patients with CRSsNP and CRSwNP, respectively, had asthma, while 1.7% and 6.6% had N-ERD, respectively. Previous studies have shown that 40 - 67% of CRSwNP patients had asthma [9, 41] and 26% N-ERD [9], while only 21.2% of CRSsNP patients registered asthma [41]. Although less common, patients with CRSsNP may present N-ERD. This has been previously reported [45] and it is explained in clinical practice by the fact that the phenotype with NP could appear later in CRS development. Although our study found a lower prevalence of coexisting T2 inflammatory diseases (47.8% in CRSsNP and 65.2% in CRSwNP), our results showed a close association between CRSwNP and more severe coexisting T2 inflammatory diseases, particularly asthma, AD, and N-ERD. Differences with other studies may be related to variations in medical practice and patients' selection process (e.g. Philpott et al. recruited patients from secondary and tertiary care centres [higher severity] whereas our study included patients from both primary care and hospital centres) [41]. Patients with CRSwNP and coexisting T2 inflammatory asthma (with or without N-ERD) present a more severe phenotype, characterised by increased number of NP, and higher NP recurrence after surgery, are more dependent on SCS, have worse asthma control and higher healthcare resource use and related costs [56].

Concerning systemic comorbidities, our study reported that arterial hypertension, diabetes mellitus (only in CRSwNP), Parkinson disease (only in CRSsNP), and dementia were more frequent in severe than non-severe disease in CRSsNP and mainly in CRSwNP patients.

Additionally, we studied the use of pharmacological treatments in CRSwNP and CRSsNP patients in Spain. Our results showed that INCS (88.3%) and oral antihistamines (51.8%) were the most prescribed drugs in CRSwNP patients. However, poor compliance of INCS has been previously reported in these patients [57]. According to the current guidelines [1, 2], INCS are recommended for CRSwNP, while oral antihistamines are only recommended in patients with comorbid AR, only present in 37% of our patients. This finding suggests an overuse of antihistamines in CRSwNP in Spain, as previously found in patients with acute rhinosinusitis [58].

According to the EPOS 2020 guidelines, antibiotics are specifically recommended only for CRSsNP [1] but our data showed that 38.1% of CRS patients were treated with antibiotics in the 2-year retrospective period (34.4% of CRSsNP vs. 59.1% of CRSwNP). This clearly differs from a German study where 12.4-19.1% of CRS patients received antibiotics during the previous year [59]. The consumption of antibiotics in Spain is traditionally higher compared to other European countries [58, 60], which could partially explain this, together with the fact that in our study we included the medications prescribed in the last two years.

Regarding SCS indicated for severe CRSwNP treatment, our study found that CRSwNP patients took an average of 2.9 cycles of SCS within one year during the two-year retrospective period, more than double of what was previously reported by Gray et al. (1.1) [61]. Patients who require more intensive SCS treatments, may be at higher risk of SCS-induced adverse events [2]. The EPOS 2020 suggested that 1-2 courses/year could be acceptable if added to INCS in patients with uncontrolled disease [1]. Additi-

onally, these guidelines indicate that novel biological treatments could be administered to patients to avoid SCS overprescription or surgery [1]. Of note, biologicals were not commercialised in Spain during the retrospective period.

Furthermore, our results showed that 48.3% patients with severe CRSwNP did not receive treatment with SCS during the retrospective period. This could point towards more than half of the patients with severe CRSwNP showing an adequate control of the disease after surgery.

It has been recently reported that patients with CRSsNP required fewer surgeries than those with CRSwNP (22.7% vs. 45.9%) [48]. The proportion of patients with CRSwNP undergoing surgery varies among countries: 43–52% in the US, 55% in the UK, 46% in Europe, and 84% in Belgium [37]. Our results showed that 41.1% of the CRSwNP patients underwent surgery, compared to 4.5% of CRSsNP patients; 89.5% of the surgeries performed in severe CRSwNP patients were ESS.
In the total 8.5-year study period, 17.3% severe CRSwNP patients had revision surgeries, similarly to the rates reported in a study with a similar duration (16.2% after 7.5 years), suggesting that a high percentage of our study population achieved adequate disease control after the surgical procedure [17]. In contrast, Calus et al., who followed their study population for longer (12 years) reported that 36.8% of their CRSwNP needed revision surgery [16]. Variations in the number of revision surgeries could be related to surgical practice, as sinonasal surgery techniques with a more extensive initial intervention improve CRS surgical management [15] and may prevent patients from undergoing revision surgeries.

### Study limitations

First, as it is inherent to cross-sectional studies based on EMRs, patient's classification may be biased due to the incorrect categorization of the disease, disease under-diagnosis, or possible inaccuracies in diagnostic coding systems, e.g. many healthcare professionals still classify NP as a different disease distinct from CRSwNP, which entails the use of different codes. We minimized this to reduce possible bias, as described in methods, but small over or underestimation may have occurred. Second, due to the unavailability of a severity score (Analogical Visual Scale) for patients with CRS and NP, EPOS 2020 recommendation criteria for antibiotics, SCS, or/and ESS were used to identify patients with severe CRSsNP or CRSwNP [1], following Sanchez Collado et al. criteria of two years [25]. This may overestimate the number of severe patients. In contrast, patients with other T2 coexistent inflammatory diseases may be receiving SCS unlinked to CRS codes, therefore, it would not appear in our analysis, and thus, patient severity could have been underestimated. Third, patients who had at least one surgery over the 8.5-year previous period were considered severe, even though the disease may have remained under control after surgery, as it can be concluded from our results on the consumption of SCS. As a result, our study may suffer from selection bias towards severe patients. Fourth, some unrecorded variables such as socioeconomic level, dose changes, or treatment adherence could influence the results. Fifth, the absence of diagnosis and prescription information from private health centres may lead to an underestimation of the number of patients with these disorders and their treatments. Finally, the diagnosis and severity of coexisting diseases in the study population was also retrospective and based on codes.

## Conclusions

This epidemiologic study performed in Spain shows that CRSsNP was more prevalent than CRSwNP, severe CRS being more common in CRSwNP than in CRSsNP patients. CRSwNP patients were also older and had higher levels of T2 inflammatory biomarkers than CRSsNP patients. CRSwNP severe patients had more specific sinonasal symptoms (including LoS) as well as coexisting T2 inflammatory diseases (asthma, AD, and N-ERD). CRSwNP severe patients also required more surgical interventions than those with CRSsNP and a non-severe disease. Overall, this may be considered the most extensive and comprehensive study describing the prevalence, CRS characteristics and coexisting T2 inflammatory diseases, in both CRSsNP and CRSwNP, in the Spanish population.

## Acknowledgements

Authors would like to thank Ignacio Hernández (Atrys Health, Madrid, Spain) for data analysis support and Dr Elena Rebollo-Gómez (Atrys Health, Madrid, Spain) for technical and medical writing support, funded by Sanofi.

## Authorship contribution

The study was conceived and designed by PIPJ and JM. Data interpretation was made by all authors. All authors drafted or critically revised and approved the final version of the submitted manuscript.

## Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital of Terrassa (Barcelona). The patient consent was not necessary, according to the Article 5 of Royal Decree 957/2020, of November 3rd, which regulates observational studies with medicines for human use.

## Conflict of interest

J. Mullol: advisory board member, research projects, and/or has received speaker fees from AstraZeneca, Genentech, GlaxoSmithKline, Lilly, Menarini, Merck Sharp & Dohme,

Mitsubishi-Tanabe Pharma, Noucor/Uriach Group, Novartis, Procter & Gamble, Regeneron Pharmaceuticals, Inc., Sanofi, UCB, Viatris/MEDA; J. Sastre: has received research funding from Sanofi and ALK, honoraria for consultancy and conferences from Novartis, Sanofi, ALK and Mundipharma; J. Dominguez-Ortega: has received funding for research, honoraria for consultancy and conferences from AstraZeneca, Chiesi and GSK, honoraria for consultancy and conferences from Bial, Novartis, Sanofi and Teva, and speaker fees from ALK, LETI Pharma and Mundipharma; M. Blanco-Aparicio: has received honoraria for consultancy and conferences from Astrazeneca, Chiesi, GSK, TEVA and Sanofi; J.A. Castillo Vizuete: advisory board member and/or has received speaker fees from Merck Sharp & Dohme, AstraZeneca, Boehringer Ingelheim, Uriach Group, GlaxoSmithKline, LETI Pharma and ALK; I. Alobid: consultant for Roche, Novartis, Salvat, Sanofi, Menarini, GSK, Viatris, and MSD; M. Garcia-Vitoria: Sanofi employee and may hold shares and/or stock options in the company; P.I. Palomo-Jiménez: Sanofi employee and may hold shares and/or stock options in the company.

## Funding

This study was funded by Sanofi.

## References

1. Fokkens WJ, Lund VJ, Hopkins C, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology. 2020;58(Suppl S29):1-464.
2. Orlandi RR, Kingdom TT, Smith TL, et al. International consensus statement on allergy and rhinology: rhinosinusitis 2021. Int Forum Allergy Rhinol. 2021;11(3):213-739.
3. Hopkins C. Chronic rhinosinusitis with nasal polyps. N Engl J Med. 2019;381(1):55-63.
4. Dietz de Loos D, Lourijsen ES, Wildeman MAM, et al. Prevalence of chronic rhinosinusitis in the general population based on sinus radiology and symptomatology. J Allergy Clin Immunol. 2019;143(3):1207-14.
5. Cho SH, Kim DW, Gevaert P. Chronic rhinosinusitis without nasal polyps. J Allergy Clin Immunol Pract. 2016;4(4):575-82.
6. Leung RM, Kern RC, Conley DB, Tan BK, Chandra RK. Osteomeatal complex obstruction is not associated with adjacent sinus disease in chronic rhinosinusitis with polyps. Am J Rhinol Allergy. 2011;25(6):401-3.
7. Stevens WW, Peters AT, Tan BK, et al. Associations between inflammatory endotypes and clinical presentations in chronic rhinosinusitis. J Allergy Clin Immunol Pract. 2019;7(8):2812-20 e3.
8. Klingler AI, Stevens WW, Tan BK, et al. Mechanisms and biomarkers of inflammatory endotypes in chronic rhinosinusitis without nasal polyps. J Allergy Clin Immunol. 2021;147(4):1306-17.
9. Laidlaw TM, Mullol J, Woessner KM, Amin N, Mannent LP. Chronic rhinosinusitis with nasal polyps and asthma. J Allergy Clin Immunol Pract. 2021;9(3):1133-41.
10. Mullol J, Azar A, Buchheit KM, Hopkins C, Bernstein JA. Chronic rhinosinusitis with nasal polyps: quality of life in the biologics Era. J Allergy Clin Immunol Pract. 2022;10(6):1434-53 e9.
11. Schneider S, Campion NJ, Villazala-Merino S, et al. Associations between the quality of life and nasal polyp size in patients suffering from chronic rhinosinusitis without nasal polyps, with nasal polyps or aspirin-exacerbated respiratory disease. J Clin Med. 2020;9(4):925 (1-12).
12. Bachert C, Zhang L, Gevaert P. Current and future treatment options for adult chronic rhinosinusitis: focus on nasal polyposis. J Allergy Clin Immunol. 2015;136(6):1431-40.
13. Cabrera-Ramirez MS, Dominguez-Sosa MS, Borkoski-Barreiro SA, Falcon-Gonzalez JC, Ramos-Macias A. Analysis and results of endoscopic sinus surgery in chronic rhinosinusitis with polyps. Acta Otorrinolaringol Esp. 2017;68(2):80-5.
14. Alobid I, Colas C, Castillo JA, et al. Spanish consensus on the management of chronic rhinosinusitis with nasal polyps (POLIposis NAsal/POLINA 2.0). J Investig Allergol Clin Immunol. 2023;33(5):317-31.
15. Arancibia C, Langdon C, Mullol J, Alobid I. Twelve-year long-term postoperative outcomes in patients with chronic rhinosinusitis with nasal polyps. Rhinology. 2022;60(2):109-17.
16. Calus L, Van Bruaene N, Bosteels C, et al. Twelve-year follow-up study after endoscopic sinus surgery in patients with chronic rhinosinusitis with nasal polyposis. Clin Transl Allergy. 2019;9:30.
17. Loftus CA, Soler ZM, Koochakzadeh S, et al. Revision surgery rates in chronic rhinosinusitis with nasal polyps: meta-analysis of risk factors. Int Forum Allergy Rhinol. 2020;10(2):199-207.
18. van der Veen J, Seys SF, Timmermans M, et al. Real-life study showing uncontrolled rhinosinusitis after sinus surgery in a tertiary referral centre. Allergy. 2017;72(2):282-90.
19. Bachert C, Bhattacharyya N, Desrosiers M, Khan AH. Burden of disease in chronic rhinosinusitis with nasal polyps. J Asthma Allergy. 2021;14:127-34.
20. Sicras-Mainar A, Enriquez JL, Hernández I, Sicras-Navarro A, Aymerich T, Leon M. Pmu146 validation and representativeness of the spanish bigpac database: integrated computerized medical records for research into epidemiology, medicines and health resource use (real word evidence). Value in Health. 2019;22(S734).
21. Sicras-Mainar A, Sicras Navarro A, Enríquez JL, et al. Validation and representativeness of the Spanish BIG-PAC database: integrated computerized medical records for research into epidemiology, medicines and health resource use (Real Word Evidence). ISPOR Europe Copenhagen 2019. Accesed on 18 October 2023.
22. Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales. 2018:119788–857.
23. International Classification of Diseases (9th edition) Clinical Modification (ICD-09-CM) [Internet]. 2021. Available from: https://eciemaps.mscbs.gob.es/ecieMaps/browser/index_9_mc.html.
24. Fokkens WJ, Lund VJ, Mullol J, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. Rhinology. 2012;50(1):1-12.
25. Sanchez-Collado I, Mora T, Munoz-Cano R, Ribo P, Mullol J, Valero A. Prevalence of chronic rhinosinusitis with nasal polyps in Catalonia (Spain): a retrospective, large-scale population-based study. Rhinology. 2022;60(5):384-96.
26. Dicker RC, Coronado F, Koo D, Parrish RG and Centers for disease control and prevention. Principles of epidemiology in public health practice; an introduction to applied epidemiology and biostatistics. 3rd ed. 2006. p. 1-512. Available from: https://stacks.cdc.gov/view/cdc/6914
27. Sociedad Española de Neumología y Cirugía Torácica. GEMA 5.3. Guía Española para el Manejo del Asma. 2023. Available from: https://www.semg.es/images/2023/documentos/GEMA_53.pdf
28. Wollenberg A, Barbarot S, Bieber T, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. J Eur Acad Dermatol Venereol. 2018;32(5):657-82.
29. World Health Organization. The anatomical therapeutic chemical classification system with defined daily doses (ATC/DDD) [Available from: https://www.who.int/standards/classifications/other-classifications/the-anatomical-therapeutic-chemical-classification-system-with-defined-daily-doses. Accesed on 8 April 2021.
30. Hastan D, Fokkens WJ, Bachert C, et al. Chronic rhinosinusitis in Europe--an underestimated disease. A GA(2)LEN study. Allergy. 2011;66(9):1216-23.
31. Hirsch AG, Stewart WF, Sundaresan AS, et al. Nasal and sinus symptoms and chronic rhinosinusitis in a population-based sample. Allergy. 2017;72(2):274-81.
32. Kim JH, Cho C, Lee EJ, Suh YS, Choi BI, Kim KS. Prevalence and risk factors of chronic rhinosinusitis in South Korea according to diagnostic criteria. Rhinology. 2016;54(4):329-35.
33. Xu Y, Quan H, Faris P, et al. Prevalence and incidence of diagnosed chronic rhinosinusitis in Alberta, Canada. JAMA Otolaryngol Head Neck Surg. 2016;142(11):1063-9.
34. Pilan RR, Pinna FR, Bezerra TF, et al. Prevalence of chronic rhinosinusitis in Sao Paulo. Rhinology. 2012;50(2):129-38.
35. Shi JB, Fu QL, Zhang H, et al. Epidemiology of chronic rhinosinusitis: results from a cross-sectional survey in seven Chinese cities. Allergy. 2015;70(5):533-9.
36. Benjamin MR, Stevens WW, Li N, et al. Clinical

characteristics of patients with chronic rhinosinusitis without nasal polyps in an academic setting. J Allergy Clin Immunol Pract. 2019;7(3):1010-6.
37. Chen S, Zhou A, Emmanuel B, Thomas K, Guiang H. Systematic literature review of the epidemiology and clinical burden of chronic rhinosinusitis with nasal polyposis. Curr Med Res Opin. 2020;36(11):1897-911.
38. Ortega-Martin L, Betancor D, Barroso B, et al. Where has all the nasal polyposis gone? J Investig Allergol Clin Immunol. 2021;31(6):500-2.
39. Raciborski F, Arcimowicz M, Samolinski B, Pinkas W, Samel-Kowalik P, Sliwczynski A. Recorded prevalence of nasal polyps increases with age. Postepy Dermatol Alergol. 2021;38(4):682-8.
40. Starry A, Hardtstock F, Wilke T, et al. Epidemiology and treatment of patients with chronic rhinosinusitis with nasal polyps in Germany-A claims data study. Allergy. 2022;77(9):2725-36.
41. Philpott CM, Erskine S, Hopkins C, et al. Prevalence of asthma, aspirin sensitivity and allergy in chronic rhinosinusitis: data from the UK national chronic rhinosinusitis epidemiology study. Respir Res. 2018;19(1):129.
42. Vaitkus J, Vitkauskiene A, Simuntis R, Vaitkus Z, Siupsinskiene N, Vaitkus S. Chronic rhinosinusitis with nasal polyps: age and disease severity differences in the levels of inflammatory markers. Medicina (Kaunas). 2021;57(3).
43. Zadeh MH, Banthia V, Anand VK and Huang C. Significance of eosinophilia in chronic rhinosinusitis. Am J Rhinol. 2002;16(6):313-7.
44. Vlaminck S, Vauterin T, Hellings PW, et al. The importance of local eosinophilia in the surgical outcome of chronic rhinosinusitis: a 3-year prospective observational study. Am J Rhinol Allergy. 2014;28(3):260-4.
45. Castillo JA, Plaza V, Rodrigo G, et al. Chronic rhinosinusitis with nasal polyps and allergic rhinitis as different multimorbid treatable traits in asthma. J Allergy Clin Immunol Glob. 2023;2(4):100134.
46. Mullol J, Marino-Sanchez F, Valls M, Alobid I and Marin C. The sense of smell in chronic rhinosinusitis. J Allergy Clin Immunol. 2020;145(3):773-6.
47. O'Quinn S, Shih VH, Martin UJ, et al. Measuring the patient experience of chronic rhinosinusitis with nasal polyposis: qualitative development of a novel symptom diary. Int Forum Allergy Rhinol. 2022;12(8):996-1005.
48. Khan A, Vandeplas G, Huynh TMT, et al. The Global Allergy and Asthma European Network (GALEN rhinosinusitis cohort: a large European cross-sectional study of chronic rhinosinusitis patients with and without nasal polyps. Rhinology. 2019;57(1):32-42.
49. Promsopa C, Kansara S, Citardi MJ, Fakhri S, Porter P, Luong A. Prevalence of confirmed asthma varies in chronic rhinosinusitis subtypes. Int Forum Allergy Rhinol. 2016;6(4):373-7.
50. Håkansson K, Thomsen SF, Konge L, Mortensen J, Backer V and von Buchwald C. A comparative and descriptive study of asthma in chronic rhinosinusitis with nasal polyps. Am J Rhinol Allergy. 2014;28(5):383-7.
51. Bengtsson C, Lindberg E, Jonsson L, et al. Chronic Rhinosinusitis Impairs Sleep Quality: Results of the GA2LEN Study. Sleep. 2017;40(1).
52. Castillo Vizuete JA, Sastre J, Del Cuvillo Bernal A, et al. Asthma, rhinitis, and nasal polyp multimorbidities. Arch Bronconeumol (Engl Ed). 2019;55(3):146-55.
53. Hassoun D, Malard O, Barbarot S, Magnan A and Colas L. Type 2 immunity-driven diseases: towards a multidisciplinary approach. Clin Exp Allergy. 2021;51(12):1538-52.
54. Hwang CS, Lee HS, Kim SN, Kim JH, Park DJ and Kim KS. Prevalence and risk factors of chronic rhinosinusitis in the elderly population of Korea. Am J Rhinol Allergy. 2019;33(3):240-6.
55. Jarvis D, Newson R, Lotvall J, et al. Asthma in adults and its association with chronic rhinosinusitis: the GA2LEN survey in Europe. Allergy. 2012;67(1):91-8.
56. Bhattacharyya N, Villeneuve S, Joish VN, et al. Cost burden and resource utilization in patients with chronic rhinosinusitis and nasal polyps. Laryngoscope. 2019;129(9):1969-75.
57. Valverde-Monge M, Barroso B, Ortega-Martin L, et al. Exploring adherence to treatment in nasal polyposis. J Investig Allergol Clin Immunol. 2022;32(4):299-301.
58. Jaume F, Quinto L, Alobid I and Mullol J. Overuse of diagnostic tools and medications in acute rhinosinusitis in Spain: a population-based study (the PROSINUS study). BMJ Open. 2018;8(1):e018788.
59. Park JJH, Seidel DU, Bachert C, Dazert S and Kostev K. Medication use in patients with chronic rhinosinusitis in Germany - a large retrospective patient-based study. Rhinology. 2019;57(2):94-100.
60. European Centre for Disease Prevention and Control. Consumption of antibacterials for systemic use (ATC group J01) in the community (primary care sector) in Europe, reporting year 2020. 2020.
61. Gray ST, Phillips KM, Hoehle LP, et al. Utilization patterns of systemic corticosteroid use for chronic rhinosinusitis. Acta Otolaryngol. 2018;138(2):153-8.

Joaquim Mullol
Rhinology Unit & Smell Clinic
ENT Department
Hospital Clínic Barcelona
FRCB-IDIBAPS, CIBERES
C/ Villarroel 170
08036 Barcelona
Spain

Tel: +34 932279872
E-mail: jmullol@clinic.cat

Joaquim Mullol[1], Joaquín Sastre[2], Javier Domínguez-Ortega[3], Marina Blanco-Aparicio[4], José Antonio Castillo Vizuete[5], Isam Alobid[6], Montse García-Vitoria[7], Paloma I. Palomo-Jiménez[8]

[1] Rhinology Unit & Smell Clinic, ENT Department, Hospital Clínic, Universitat de Barcelona, FRCB-IDIBAPS, CIBERES, Barcelona, Catalonia, Spain

[2] Department of Allergology, Fundación Jiménez Díaz, CIBER de Enfermedades Respiratorias (CIBERES), Facultad de Medicina, Universidad Autónoma de Madrid, Madrid, Community of Madrid, Spain

[3] Department of Allergology, La Paz University Hospital, Institute for Health Research (IdiPAZ), Madrid, Community of Madrid, Spain

[4] Asthma Unit, La Coruña University Hospital, La Coruña, Galicia, Spain

[5] Department of Respiratory Medicine, Hospital Universitari Dexeus, Barcelona, Catalonia, Spain

[6] Rhinology and Skull Base Unit, ENT Department, Hospital Clinic, Universitat de Barcelona, FRCB-IDIBAPS, CIBERES, Barcelona, Catalonia, Spain

[7] Sanofi, Barcelona, Catalonia, Spain

[8] Sanofi, Madrid, Community of Madrid, Spain

**Rhinology 62: 4,** 421 - 431, 2024
https://doi.org/10.4193/Rhin23.341

**Received for publication:**
September 14, 2023
**Accepted:** April 15, 2024

**Assocociate Editor:** Sietze Reitsma

**This manuscript contains online supplementary material**

## SUPPLEMENTARY MATERIAL

Table S1. Inclusion and exclusion criteria.

| Inclusion criteria | Exclusion criteria |
|---|---|
| a) age ≥18 years | a) displaced or out-of-area patients |
| b) patients with diagnosis established by CRS and/or NP codes before the index date | b) patients permanently institutionalized (in nursing homes) |
| c) patients with ≥2 health records for a minimum of 24 months prior to index date | c) patients terminally ill and/or severely mentally ill |
| d) patients with ≥2 prescriptions during the observation period | |
| e) patients with ≥2 health records during the observation period. | |
| f) patients with a CRS diagnosis record prior to 01/07/2018 | |

Table S2. Definitions of severity according to chronic rhinosinusitis phenotypes.

| | Definition |
|---|---|
| Severe CRSsNP | Patients who received treatment with:<br>a) long courses of antibiotics (≥1 month; Anatomical Therapeutic Chemical [ATC] Classification System code J01, antibacterials for systemic use) during the last 2 years; and/or<br>b) Sinonasal surgery during the study period (ICD-9-CM codes 21.31, 22.4, 22.5, 22.6 [excluded: 22.61], 22.9). |
| Severe CRSwNP | Patients who received treatment with:<br>a) ≥2 short courses of oral or systemic corticosteroids (≥ 5 days) during the last 2 years (ATC code: H02AB; courses: 5–30-day pattern in a row, with at least 15 days between courses); and/or<br>b) Sinonasal surgery during the study period (ICD-9-CM codes 21.31, 22.4, 22.5, 22.6 [excluded: 22.61], 22.9). |

Abbreviations: CRSsNP: chronic rhinosinusitis without nasal polyps; CRSwNP: chronic rhinosinusitis with nasal polyps.

Table S3. Diagnostic codes for the different chronic rhinosinusitis characteristics.

| Disorders | ICD-09-CM codes |
|---|---|
| Chronic rhinosinusitis (CRSsNP) | 473.0, 473.2, 473.8, 473.9 |
| Nasal polyposis (CRSwNP) | 471.0, 471.9 |
| **Sinonasal symptoms** | |
| Rhinorrhea/nasal obstruction | 478.19 |
| Loss of smell | 781.1 |
| Sleep disorders | 780.5, 307 |
| **Type 2 inflammatory diseases** | |
| Allergic rhinitis | 477 |
| Asthma | 493 |
| Atopic dermatitis | 691. 8, 692.9 |
| N-ERD | 473.0, 473.2, 473.8, 473.9 [CRS] + 493 [asthma] + (995.27 + E935.3 [salicylates], E935.5 [pyrazole derivatives], E935.6 [antirheumatics]; or V14.6 [intolerance to NSAID]) |
| **Sinonasal surgeries** | 21.31, 22.4, 22.5, 22.6 [excluded: 22.61], 22.9 |

Abbreviations: CRSsNP: chronic rhinosinusitis without nasal polyps; CRSwNP: chronic rhinosinusitis with nasal polyps; N-ERD: aspirin/non-steroidal anti-inflammatory drugs exacerbated respiratory disease. Source: Spanish Ministry of Health, 2021 [23].