



A real-world assessment of asthma with chronic rhinosinusitis

Fabio Luigi Massimo Ricciardolo, MD, PhD, FERS^{*}; Stefano Levra, MD^{*};
Andrea Elio Sprio, PhD[†]; Francesca Bertolini, PhD[†]; Vitina Carriero, PhD[‡];
Fabio Gallo, PhD[‡]; Giorgio Ciprandi, MD[§]

^{*} Department of Clinical and Biological Sciences, University of Turin, San Luigi Gonzaga University Hospital, Turin, Italy

[†] Department of Clinical and Biological Sciences, University of Turin, Turin, Italy

[‡] Department of Health Science, University of Genoa, Genoa, Italy

[§] Allergy Clinic, Casa di Cura Villa Montallegro, Genoa, Italy

ARTICLE INFO

Article history:

Received for publication January 13, 2020.

Received in revised form March 3, 2020.

Accepted for publication March 5, 2020.

ABSTRACT

Background: Chronic rhinosinusitis (CRS) includes 2 main phenotypes: CRS without nasal polyps (CRSsNP) and CRS with nasal polyps (CRSwNP). CRS has been reported to be a comorbidity of asthma.

Objective: This study aimed to investigate the role of CRS in outpatients with asthma visited in real-world setting.

Methods: This cross-sectional study enrolled 499 consecutive outpatients with asthma. Age, sex, body mass index, smoking status, lung function, Asthma Control Test, inflammatory type 2 biomarkers (including fractional exhaled nitric oxide, blood eosinophils, serum total immunoglobulin E, and allergy), treatment step according to the Global Initiative for Asthma, and comorbidities (obstructive sleep apnea syndrome, arterial hypertension, bronchiectasis, diabetes mellitus type 2, and osteoporosis) were evaluated.

Results: A total of 179 (35.87%) patients had CRS, in particular 93 (18.64%) had CRSsNP and 86 (17.23%) had CRSwNP. Type 2 inflammation (defined by at least 1 positive biomarker) was present in 81.44% of patients (fractional exhaled nitric oxide > 30 parts per billion in 46.9%, blood eosinophil count > 300 cell/ μ L in 39.67%, serum total immunoglobulin E > 100 IU/mL in 51.54%, and allergy in 53.71%). By multivariate analysis, type 2 inflammation and blood eosinophils greater than 300 cell/ μ L were the main predictors (odds ratio [OR] 2.54 and 2.26, respectively) of CRS-asthma association. In particular, CRSwNP comorbidity was predicted by type 2 inflammation (OR 3.4) and blood eosinophils greater than 300 cell/ μ L (OR 3.0). Smoking had conflicting outcome.

Conclusion: This study confirmed that CRS is a frequent asthma comorbidity because it affects more than one-third of outpatients with asthma. CRSwNP is associated with type 2 inflammation and blood eosinophilia. These outcomes underline that CRSwNP asthma phenotype deserves adequate attention for careful management and optimal identification of the best-tailored therapy.

© 2020 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

Chronic rhinosinusitis (CRS) affects approximately 10% to 12% of the European population.¹ CRS may be classified into 2 phenotypes based on endoscopy and computed tomography (CT) findings: CRS with nasal polyposis (CRSwNP) and CRS without nasal polyposis (CRSsNP).² CRSwNP is defined by presence of nasal polyps and signs and symptoms lasting longer than 8 to 12 weeks.^{3,4} Nasal

polyps are benign edematous masses in nasal cavities, paranasal cavities, or both. Their occurrence depends on an exaggerated inflammatory reaction. As nasal polyps occupy space into nasal cavities, they can cause nasal obstruction, rhinorrhea, postnasal drip, and hyposmia or anosmia.⁵ The CRSwNP overall prevalence is approximately estimated to be 2% to 4% of the general population. Approximately 30% of patients who have CRSwNP have asthma.⁶ Patients with both diseases have poor therapeutic response and high recurrence rate, so the disease is more severe and difficult to treat.⁷ CRSwNP and asthma share severe impairment of quality of life and cause significant financial burden for society.³

Recent technological advances, mainly in the fields of genetics and engineering, increased information concerning phenotypes and endotypes of chronic respiratory disorders, generally about

Reprints: Fabio Luigi Massimo Ricciardolo, MD, PhD, FERS, San Luigi Gonzaga University Hospital, University of Torino, Department of Clinical and Biological Sciences, Regione Gonzole 10, 10043 Orbassano (Torino), Italy; E-mail: fabioluigimassimo.ricciardolo@unito.it.

Disclosures: The authors have no conflicts of interest to report.

Funding Sources: The authors have no funding sources to report.

<https://doi.org/10.1016/j.anai.2020.03.004>

1081-1206/© 2020 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

type of inflammation and immune response.^{8–11} This information could enable more targeted, effective, and efficient precision medicine (PM). PM refers to the “ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease, in the biology or prognosis of those diseases they may develop, or in their response to a specific treatment.”¹² Consequently, PM allows us to stratify patients into subgroups and to tailor treatment based on their peculiar pheno-endotypes.¹³ This approach has been defined as personalized medicine.¹⁴

On the basis of this background, we aimed to assess CRS in a group of patients with asthma recruited in a real-world setting to define the prevalence of the CRS phenotypes and identify potential predictive factors associated with CRS comorbidity in asthma. In this regard, the definition of a particular asthma phenotype could be useful in clinical practice because it could pave new therapeutic strategies using biologics.

Methods

Patients

For this observational cross-sectional study, 499 patients with asthma were enrolled at the San Luigi Gonzaga University Hospital (Orbassano, Torino, Italy). They were outpatients, who were referred to an asthma clinic for a specialist visit and were sequentially recruited. Written informed consent was obtained from each subject. The study conformed to the Declaration of Helsinki and was approved by the local ethics committees (San Luigi Gonzaga University Hospital: protocol 4478/2017). Clinical data and patient history were obtained at recruitment. The visit included history, clinical examination, body mass index measurement, spirometry, fractional exhaled nitric oxide (FeNO) measurement, skin prick test, blood sampling (for eosinophil and neutrophil count and total immunoglobulin E [IgE] value), Asthma Control Test (ACT) questionnaire, and treatment step level, from step 1 (short-term or periodic use of low-dose inhaled corticosteroid [ICS]) to step 5 (at least long-term use of high-dose ICS: fluticasone propionate > 500 µg plus long-acting β-agonists), according to the Global Initiative for Asthma document.¹⁵

Study Design and Setting

Asthma diagnosis was previously established and documented as well as CRS and allergy diagnosis. Inclusion criteria were adulthood and documented asthma diagnosis, based on typical symptoms history consistent with reversibility to bronchodilators and/or bronchial hyperresponsiveness to methacholine. Exclusion criteria were a history of lung disease other than asthma, coronary artery disease, congestive heart failure, or *cor pulmonale*, recent asthma exacerbation, presence of acute (in the last 4 weeks) or chronic upper and/or lower respiratory tract infections. Patients discontinued the use of short-acting and long-acting bronchodilators 12 hours before lung function measurement.

The presence of comorbidity, including allergy, arterial hypertension, obstructive sleep apnea syndrome, diabetes mellitus type 2, bronchiectasis, and osteoporosis, was investigated.

White blood cell (WBC) count and WBC differential count were performed based on optical and impedance characteristics using a Cell-Dyn Sapphire (Abbott, Rome, Italy) automated hematology analyzer (data were expressed as an absolute number).

Functional Assessment

Pulmonary function test was performed assessing spirometry and lung volumes using body plethysmograph (Vmax Encore 62, Carefusion, Germany), as stated by the European Respiratory Society.¹⁶

Table 1

Demographic and Clinical Characteristics of Study Participants (N = 499)

Characteristic	Overall
Age (y)	58.25 ± 15.07
Sex	
Women	301 (60.32%)
Men	198 (39.68%)
BMI	26.84 ± 5.48
Smoking	
Never smoker	274 (54.91%)
Past smoker	175 (35.07%)
Current smoker	50 (10.02%)
Age at asthma onset (y)	37.03 ± 18.96
Chronic rhinosinusitis	179 (35.87%)
CRS without nasal polyps	93 (18.64%)
CRS with nasal polyps	86 (17.23%)
Age at onset	37.03 ± 18.96
FVC	100.11 ± 18.08
FEV ₁	83.94 ± 21.2
FEV ₁ /FVC	81.78 ± 13.5
ACT	20.66 ± 3.66
Treatment step (GINA)	
1	63 (12.63%)
2	47 (9.42%)
3	162 (32.46%)
4	115 (23.05%)
5	112 (22.44%)
Blood neutrophils (cells/µL)	4272 ± 1713
Blood neutrophils (cells/µL)	
≤4000	153 (53.5%)
>4000	133 (46.5%)
Type 2 inflammation	395 (81.44%)
Blood eosinophils (cells/µL)	310.9 ± 249.6
Blood eosinophils (cells/µL)	
≤300	257 (60.33%)
>300	169 (39.67%)
FeNO ppb	38.63 ± 31.25
FeNO ppb	
≤30	214 (53.10%)
>30	189 (46.90%)
Total IgE (IU/mL)	286.8 ± 543.6
Total IgE (IU/mL)	
≤100	142 (48.46%)
>100	151 (51.54%)
Allergy	268 (53.71%)
Poly-allergy	226 (45.29%)
Allergy to perennial allergens	193 (38.68%)
OSAS	26 (5.21%)
Arterial hypertension	159 (31.86%)
Bronchiectasis	36 (7.21%)
Diabetes mellitus type 2	33 (6.61%)
Osteoporosis	39 (7.82%)

Abbreviations: ACT, Asthma Control Test; BMI, body mass index; CRS, chronic rhinosinusitis; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GINA, Global Initiative for Asthma; IgE, immunoglobulin E; OSAS, obstructive sleep apnea syndrome.

NOTE. The results are expressed as mean with standard deviation or as number of subjects with percentage. The characteristics reported in the table concern the data available in the database.

Nitric Oxide Measurement

FeNO was measured with a chemiluminescence analyzer (Eco Medics CLD88 sp, Duernten, Switzerland); the detection limit of the apparatus was 1 to 5 parts per billion (ppb), as required by the American Thoracic Society guidelines, with a resolution of 1 ppb. The analyzer was calibrated daily using a certified nitric oxide (NO) mixture. Exhaled NO was recorded with the single-breath method according to published guidelines.¹⁷

Asthma Control Test

The ACT questionnaire consisted of 5 questions with 5 possible responses, exploring the patient's perception of his/her asthma control.¹⁸ The result could range between 0 and 25, in which 25 was

Table 2

Contingency Tables and Output of the Univariate Analysis (N = 499)

Characteristic	Descriptive statistic		Univariate analysis	
	CRS		OR (95% CI)	P value
	No (320 (64.13%))	Yes (179 (35.87%))		
BMI	27.15 ± 5.78	26.29 ± 4.89	0.97 (0.94-1.01)	.11
Age	58.1 ± 15.59	58.53 ± 14.13	1 (0.99-1.01)	.76
Age at onset	36.94 ± 19.66	37.17 ± 17.71	1 (0.99-1.01)	.90
Sex				.71
Men	125 (39.06%)	73 (40.78%)	1.07 (0.74-1.56)	
Smoking ^a				.04
Never smoker	178 (55.62%)	96 (53.63%)	1	
Past smoker	103 (32.19%)	72 (40.22%)	1.3 (0.88-1.91)	
Current smoker	39 (12.19%)	11 (6.15%)	0.52 (0.25-1.04)	
Treatment step ^a				.04
1	45 (14.06%)	18 (10.06%)	1	
2	31 (9.69%)	16 (8.94%)	1.29 (0.57-2.92)	
3	108 (33.75%)	54 (30.17%)	1.25 (0.67-2.4)	
4	78 (24.38%)	37 (20.67%)	1.19 (0.61-2.36)	
5	58 (18.12%)	54 (30.17%)	2.33 (1.22-4.58)	
ACT	20.71 ± 3.6	20.57 ± 3.76	0.99 (0.94-1.04)	.68
FVC	99.9 ± 18.11	100.49 ± 18.07	1 (0.99-1.01)	.73
FEV ₁	84.36 ± 21.09	83.21 ± 21.44	1 (0.99-1.01)	.56
FEV ₁ /FVC	82.47 ± 12.98	80.49 ± 14.39	0.99 (0.97-1)	.15
Blood neutrophils (cells/ μ L)	4308 ± 2059	4377 ± 1795		.83
Blood neutrophils (cells/ μ L) > 4000 ^a	77 (43.02%)	56 (52.34%)	1.45 (0.90-2.36)	.13
Type 2 inflammation ^a	234 (75.97%)	161 (90.96%)	3.18 (1.83-5.84)	<.001
Blood eosinophils (cells/ μ L)	280.6 ± 221.3	410.1 ± 299.3		<.001
Blood eosinophils (cells/ μ L) > 300 ^a	81 (30.22%)	88 (55.7%)	2.90 (1.93-4.38)	<.001
FeNO ppb ^a	33.88 ± 31.16	45.91 ± 30.07	1.01 (1.01-1.02)	<.001
FeNO ppb >30	92 (37.70%)	97 (61.01%)	2.58 (1.72-3.87)	<.001
Total IgE (IU/mL)	307.0 ± 501.4	363.0 ± 701.5		.57
Total IgE (IU/mL) > 100	84 (48.55%)	67 (55.83%)	1.34 (0.84-2.14)	.22
OSAS	17 (5.31%)	9 (5.03%)	0.94 (0.39-2.12)	.89
Arterial hypertension	107 (33.44%)	52 (29.05%)	0.82 (0.55-1.21)	.31
Bronchiectasis	23 (7.19%)	13 (7.26%)	1.01 (0.49-2.02)	.97
Allergy	179 (55.94%)	89 (49.72%)	0.81 (0.56-1.17)	.26
Polyallergy	156 (48.75%)	70 (39.11%)	0.7 (0.48-1.01)	.06
Allergy to perennial allergens	129 (40.31%)	64 (35.75%)	0.85 (0.58-1.24)	.40
Diabetes mellitus type 2	17 (5.31%)	16 (8.94%)	1.78 (0.87-3.64)	.11
Osteoporosis	27 (8.44%)	12 (6.7%)	0.8 (0.38-1.58)	.52

Abbreviations: ACT, Asthma Control Test; BMI, body mass index; CRS, chronic rhinosinusitis; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; IgE, immunoglobulin E; OR, odds ratio; OSAS, obstructive sleep apnea syndrome.

NOTE. Characteristic: variable taken into account; P value, likelihood ratio P value. The characteristics reported in the table concern the data available in the database.

P values <.05 are represented in bold.

^aVariables entering the multivariate analysis (see the text for abbreviations and further details).

the optimal asthma control and less than 20 was poor asthma control.

Allergy

Allergy was considered if there was a documented sensitization, assessed by skin prick test and/or measurement on serum allergen-

specific IgE, and demonstration of a cause/effect relationship between exposure to sensitizing allergen and symptom occurrence. Patients with allergy to more than or equal to 2 allergens have been considered as polyallergy.¹⁹

Type 2 Inflammation

Type 2 inflammation was defined when at least 1 type 2 high factor was positive, including blood eosinophil count greater than 300 cells/ μ L, FeNO greater than 30 ppb, total IgE greater than 100 IU/mL, and allergy.^{20,21}

Chronic Rhinosinusitis

CRS was diagnosed on the basis of the validated guidelines.³

Statistical Analysis

Continuous variables were given as means with SDs and categorical variables as the number of subjects and percentage values. Both dichotomy CRS (absence or presence) and 3-class CRS (absence, CRSwNP, and CRSsNP) were considered as the primary outcome.

The univariate logistic regression and the multinomial logistic regression model (where appropriate) were performed to screen the effect of clinical and demographic variables on CRS. The odds

Table 3

Multivariate Analysis, the Predictor Effects on Chronic Rhinosinusitis

Characteristic	OR (95% CI)	P value
Type 2 inflammation		<.01
No	1	
Yes	2.54 (1.32-5.17)	
Blood eosinophils (cells/ μ L)		<.001
≤300	1	
>300	2.26 (1.46-3.54)	
Smoking		<.01
Never smokers	1	
Past smokers	1.59 (1.03-2.47)	
Current smoker	0.42 (0.16-0.97)	

NOTE. Results are expressed as odds ratio (OR) with 95% CI; P value, likelihood ratio P value.

P values <.05 are represented in bold.

Table 4

Contingency Tables and Output of the Univariate Analysis (N = 499)

Characteristic	Descriptive statistic			Univariate analysis		
	CRS			CRS without nasal polyps vs none	CRS with nasal polyps vs none	P value
	None (320 (64.13%))	CRS without nasal polyps (93 (18.64%))	CRS with nasal polyps (86 (17.23%))			
BMI	27.15 ± 5.78	26.69 ± 5.52	25.82 ± 4.02	0.99 (0.94-1.03)	0.96 (0.91-1.01)	.16
Age	58.1 ± 15.59	59.24 ± 15.22	57.76 ± 12.89	1.01 (0.99-1.02)	1 (0.98-1.01)	.77
Age at asthma onset	36.94 ± 19.66	37.53 ± 18.26	36.78 ± 17.19	1 (0.99-1.01)	1 (0.99-1.01)	.96
Sex						.63
Men	125 (39.06%)	35 (37.63%)	38 (44.19%)	0.95 (0.59-1.51)	1.24 (0.76-1.99)	
Smoking ^a						<.01
Never smoker	178 (55.62%)	43 (46.24%)	53 (61.63%)	1	1	
Past smoker	103 (32.19%)	41 (44.09%)	31 (36.05%)	1.65 (1.01-2.69)	1.02 (0.61-1.67)	
Current smoker	39 (12.19%)	9 (9.68%)	2 (2.33%)	0.99 (0.43-2.09)	0.21 (0.04-0.66)	
Treatment step						.11
1	45 (14.06%)	12 (12.9%)	6 (6.98%)	1	1	
2	31 (9.69%)	6 (6.45%)	10 (11.63%)	0.75 (0.25-2.1)	2.33 (0.81-7.2)	
3	108 (33.75%)	29 (31.18%)	25 (29.07%)	0.99 (0.48-2.15)	1.65 (0.68-4.5)	
4	78 (24.38%)	18 (19.35%)	19 (22.09%)	0.86 (0.39-1.95)	1.74 (0.7-4.87)	
5	58 (18.12%)	28 (30.11%)	26 (30.23%)	1.77 (0.83-3.93)	3.17 (1.3-8.77)	
ACT	20.71 ± 3.6	20.34 ± 3.77	20.82 ± 3.76	0.97 (0.92-1.04)	1.01 (0.94-1.08)	.64
FVC	99.9 ± 18.11	98.35 ± 18.18	102.8 ± 17.77	1 (0.98-1.01)	1.01 (0.99-1.02)	.24
FEV ₁	84.36 ± 21.09	81.86 ± 21.58	84.68 ± 21.32	0.99 (0.98-1.01)	1 (0.99-1.01)	.57
FEV ₁ /FVC	82.47 ± 12.98	80.59 ± 13.7	80.36 ± 15.29	0.99 (0.97-1.01)	0.99 (0.97-1.01)	.35
Blood neutrophils (cells/ μ L)	4308 ± 2059	4404 ± 2064	4346 ± 1434			.96
> 4000	77 (43.02%)	29 (50%)	27 (55.1%)	1.32 (0.73-2.39)	1.62 (0.86-3.06)	.27
Type 2 inflammation ^{a,b,c}	234 (75.97%)	81 (87.1%)	80 (95.24%)	2.07 (1.12-4.13)	5.68 (2.36-17.68)	<.001
Blood eosinophils (cells/ μ L)	280.6 ± 221.3	352.4 ± 261.4	478.9 ± 327.8			<.001
>300 ^{a,b,c,d}	81 (30.22%)	41 (47.67%)	47 (65.28%)	2.1 (1.28-3.45)	4.29 (2.5-7.49)	<.001
FeNO ppb ^a	33.88 ± 31.16	39.83 ± 29.03	52.56 ± 29.95	1.01 (0.99-1.02)	1.02 (1.01-1.03)	<.001
>30 ^{b,c}	92 (37.70%)	46 (55.42%)	51 (67.10%)	2.05 (1.26-3.42)	3.37 (1.94-5.75)	<.001
>50	49 (20.1%)	23 (27.7%)	38 (50%)	1.53 (0.85-2.71)	3.98 (2.30-6.94)	<.001
Total IgE (IU/mL)	307.0 ± 501.4	403.1 ± 849.4	313.3 ± 459.6			.64
>100	84 (48.55%)	35 (53.03%)	32 (59.26%)	1.19 (0.68-2.11)	1.53 (0.83-2.85)	.37
Allergy	179 (55.94%)	42 (45.16%)	47 (54.65%)	0.68 (0.43-1.07)	0.99 (0.62-1.59)	.24
Polyallergy	156 (48.75%)	32 (34.41%)	38 (44.19%)	0.58 (0.35-1.01)	0.86 (0.54-1.39)	.07
Allergy to perennial allergens	129 (40.31%)	34 (36.56%)	30 (34.88%)	0.88 (0.55-1.41)	0.82 (0.5-1.34)	.68
OSAS	17 (5.31%)	2 (2.15%)	7 (8.14%)	0.47 (0.09-1.54)	1.64 (0.63-3.86)	.17
Arterial hypertension	107 (33.44%)	28 (30.11%)	24 (27.91%)	0.86 (0.52-1.41)	0.78 (0.46-1.3)	.57
Bronchiectasis	23 (7.19%)	5 (5.38%)	8 (9.3%)	0.79 (0.27-1.92)	1.37 (0.57-3.02)	.60
Diabetes mellitus	17 (5.31%)	7 (7.53%)	9 (10.47%)	1.53 (0.59-3.61)	2.17 (0.91-4.87)	.22
type 2						
Osteoporosis	27 (8.44%)	7 (7.53%)	5 (5.81%)	0.94 (0.38-2.09)	0.73 (0.26-1.77)	.73

Abbreviations: ACT, Asthma Control Test; BMI, body mass index; CRS, chronic rhinosinusitis; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; IgE, immunoglobulin E.

NOTE. Characteristic: variable taken into account; P value, likelihood ratio P value. The characteristics reported in the table concern the data available in the database. P values <.05 are represented in bold.

^aVariables entering the multivariate analysis (see the text for abbreviations and further details).

^bNone vs CRSsNP.

^cNone vs CRSwNP.

^dCRSsNP vs. CRSwNP.

ratios (ORs) associated with CRS were calculated with their 95% CI for each factor from the logistic and penalized multinomial logistic model. The Likelihood Ratio Test was used as a test of statistical significance.

Those covariates with a P value lesser than .05 were then selected for the multivariate analysis, in which CRS was the dependent variable. Multivariate analysis was performed using both logistic regression and multinomial logistic regression models again. Model selection was made by the Akaike Information Criterion.

The multivariate model performance was assayed using k-fold cross-validation. In particular, the dataset was split into a training set (95% of the data) and a test set (5% of the data) randomly for k different times, and then the percentage of total items was classified correctly, and false-positive and false-negative rates were estimated using confusion matrix.

Owing to the exploratory design of this study, no adjustment for multiple testing was performed. Differences, with a P value less than .05, were selected as significant, and data were acquired and analyzed in R version 3.6.1 software environment.

Results

This study included 499 (198 men) patients. The demographic and clinical characteristics of the patients are summarized in Table 1. Briefly, the mean age was 58.25 years. Although most patients were never smokers, 175 (35.07%) and 50 (10.02%) patients were past or current smokers, respectively. Regarding the primary outcome, 179 (35.87%) patients had CRS, of whom 86 (17.23%) had CRSwNP, whereas 93 (18.64%) had CRSsNP. Grade 5 treatment step accounted for 112 (22.44%) patients. Concerning asthma phenotyping, type 2 inflammation was present in most of the patients

Table 5
Multivariate Analysis, the Predictor Effects on Chronic Rhinosinusitis

Characteristic	CRS without nasal polyps vs none	CRS with nasal polyps vs none	P value
Type 2 inflammation			<.01
No	1	1	
Yes	2.43 (1.12–5.83)	3.41 (1.18–13.21)	
Blood eosinophils (cells/ μ L)			<.01
≤ 300	1	1	
> 300	1.7 (0.99–2.94)	3.05 (1.71–5.6)	
Smoking			<.01
Never smokers	1	1	
Past smokers	1.89 (1.1–3.24)	1.31 (0.73–2.34)	
Current smokers	0.9 (0.33–2.18)	0.07 (0–0.55)	

Abbreviation: CRS, chronic rhinosinusitis.

NOTE. Results are expressed as odds ratio with 95% CI; P value, likelihood ratio P value.

P values $<.05$ are represented in bold.

(395 subjects; 81.44%); 169 (39.67%) had blood eosinophil count of greater than 300 cells/ μ L, 189 (46.90%) had FeNO greater than 30 ppb, 151 (51.54%) had serum total IgE greater than 100 IU/mL, and 268 (53.71%) had allergy. Among these, 226 (45.29%) had polyallergy, and 193 (38.68%) had allergy to perennial allergens. Lung function mean values were in the normal reference ranges. The mean ACT score was 20.66. Regarding blood neutrophils, 133 (46.5%) patients had high levels.

Concerning other asthma comorbidities, arterial hypertension and bronchiectasis were detected in 31.86% of patients, whereas 7.82% had osteoporosis, 6.61% had diabetes mellitus type 2, and 5.21% had obstructive sleep apnea syndrome.

Regarding dichotomy CRS, the descriptive statistics of demographic and clinical factors in the levels of CRS are reported in Table 2. The mean age in patients without CRS was 58.1 years, whereas those with CRS had an average age of 58.53 years. Type 2 inflammation was present in 75.97% of patients without CRS and in 90.96% of those with CRS. Blood eosinophil count was more than 300 cells/ μ L in 30.22% of patients without CRS and in 55.70% of those with CRS; FeNO was more than 30 ppb in 37.70% and 61.01% of patients without and with CRS, respectively; serum total IgE was more than 100 IU/mL in 48.55% of patients without CRS and in 55.83% of those with CRS; allergy was detected in 55.94% of patients without CRS and in 49.72% of the affected ones. The univariate logistic regression analysis (Table 2), using the complete set of data, demonstrated a significant association among smoking status, asthma treatment step, type 2 inflammation, FeNO, blood eosinophils, and CRS (P values $<.05$). The multivariate analysis (Table 3) confirmed a statistically significant effect of current smoking, type 2 inflammation, and blood eosinophil count of more than 300 cells/ μ L on CRS (P values: .003, .005, and $<.001$, respectively). In particular, the ORs were 2.54 for type 2 inflammation, 2.26 for blood eosinophil count more than 300 cells/ μ L, 1.59 for past smoking, and 0.42 for current smoking. The multivariate model performance showed a good model average accuracy (95% CI = 0.63). Moreover, low false-positive and false-negative rates were 0.1 and 0.26, respectively.

Regarding the comparison between CRSwNP and CRSsNP, the descriptive statistics of demographic and clinical factors in the levels of CRS are reported in Table 4. The univariate multinomial logistic regression analysis (Table 4), using the complete set of data, demonstrated a significant difference between the two asthma-CRS phenotypes, individually compared with asthma without CRS phenotype, concerning smoking status ($<.01$), type 2 inflammation ($<.001$), blood eosinophil count of more than 300 cells/ μ L ($<.001$), FeNO ($<.001$), and CRS.

The multivariate analysis (Table 5) confirmed a statistically significant effect of smoking, type 2 inflammation, and blood

eosinophils on CRS (P values: $<.01$, $<.01$, and $<.01$, respectively). Comparing patients with asthma-CRSsNP vs those with asthma alone and those with asthma-CRSwNP vs those with asthma alone, the ORs for type 2 inflammation were 2.43 and 3.41 respectively; the ORs for blood eosinophil count of more than 300 cells/ μ L were 1.7 and 3.05, respectively; the ORs for past smoking were 1.89 and 1.31, respectively, and the ORs for current smoking were 0.9 and 0.07, respectively. Finally, the multivariate model performance showed a good model average accuracy (95% CI = 0.62), and the low false-positive and false-negative rates were 0.01 and 0.03, respectively.

Discussion

Asthma, a heterogeneous chronic inflammatory airway disease, has a high prevalence, ranging between 5% and 10% of the general population.²² Asthma frequently is associated with several comorbidities, including upper airway diseases, such as rhinitis and rhinosinusitis.^{23,24} In particular, the CRSwNP-asthma phenotype is particularly severe and needs careful management.⁷ Therefore, pheno/endotyping-based guidelines are indispensable in clinical practice to tailor the best treatment for every patient. However, the bulk of the evidence on this topic derives from studies recruiting selected people with asthma whose results have limited applicability as these do not reflect what is commonly observed in clinical practice.²⁵ Indeed, high-level evidence derived from selected subjects could not concern all patients. There is consequently the need to recruit an asthma population in a real-world setting. This real-life study provided findings that may faithfully mimic the daily medical activity on outpatients with asthma.

The primary outcome showed that 35.9% of the patients with asthma had CRS, in particular, 18.6% had CRSsNP and 17.2% CRSwNP. These findings are consistent with the literature that reports an NP prevalence ranging from 10% to 30% in mild asthma to 70% to 90% in severe asthma, even though the reported ranges were particularly large.^{7,26}

Moreover, additional information concerned the high prevalence of grade 5 of asthma treatment step ($>22\%$) and of past/current smoking ($>45\%$). Type 2 inflammation (evidence of at least 1 type 2 high factor) concerned more than 80% of the patients. More than half of the patients were allergic (interestingly polyallergy and allergy to perennial allergens were common), 51.5% had high total IgE levels, approximately 40% had more than 300 blood eosinophils, and 47% had a mean FeNO value of more than 30 ppb. These data confirm the frequent involvement of type 2 immune response in patients with asthma as widely reported.^{27–30} Arterial hypertension and bronchiectasis affected approximately one-third of our patients, osteoporosis approximately 8%, and diabetes mellitus type 2 approximately 6%. These comorbidities have been reported clinically relevant because they are associated with increased systemic corticosteroid bursts in frequent exacerbators,³¹ namely patients with 2 or more asthma exacerbations per year.³²

This study provided other interesting results concerning the identification of factors associated with CRS comorbidity in asthma. In this regard, we performed 2 separate analyses: the first subdivided the population into 2 subgroups, such as patients with CRS or without CRS, and the second considered separately patients with CRSwNP and CRSsNP, comparing these patients with asthma alone.

The first step demonstrated that smoking, asthma treatment step, type 2 inflammation, blood eosinophil count of more than 300 cells/ μ L, and high FeNO ppb were significantly associated with CRS in people with asthma at the univariate analysis. The multivariate model restricted the significant factors to type 2 inflammation, blood eosinophils, and smoking. Type 2 inflammation, including eosinophilia, marks the predominant asthma-CRS phenotype, even though different subphenotypes have been identified.³³ This finding

underlines the relevance of type 2 inflammation in the definition of the asthma-CRS phenotype. The presence of type 2 inflammation, in particular of blood eosinophilia, more than doubled the probability of observing the asthma-CRS phenotype in this population. However, the findings of smoking are conflicting because past smoking seems to be a risk factor, whereas current smoking is protective. However, these data should be prudently interpreted considering the limited number of smokers with CRS in this sample.

The second step initially confirmed the relevance of the same variables. The multivariate analysis identified 4 factors, such as type 2 inflammation and blood eosinophils, past and current smoking, associated with CRS comorbidity, considering separately both CRS phenotypes. However, CRSsNP was significantly associated with asthma in the presence of type 2 inflammation (OR 2.43) and past smoking (OR 1.89). The other variables displayed wide confidence intervals, such as including the 1 value, which dampened the relevance of findings. In contrast, the CRSwNP-asthma phenotype was significantly associated with type 2 inflammation (OR 3.41), blood eosinophil count of more than 300 cells/ μ L (OR 3.05), and FeNO more than 50 ppb (OR 3.98). Notably, current smoking was also significantly associated, but only 2 patients belonged to this phenotype, so this outcome could not be considered trustworthy.

Therefore, this study outlined the relevance of type 2 inflammation in pointing out the asthma-CRS phenotype. The practical consequence of this evidence is the possibility of choosing well-defined biologics for treating people with asthma with CRS.³⁴ Of course, the choice of the more appropriate biologic should be based on carefully endotyping as different CRSwNP endotypes exist.³⁵

In this regard, blood eosinophils are very important in clinical practice because as has been reported blood eosinophil count may be used to predict frequent asthma exacerbations.³⁶ Consistently, this study confirmed that type 2 inflammation, mainly concerning blood eosinophilia, was the leading predictor of CRSwNP comorbidity in outpatients with asthma. This finding highlights the clinical relevance of CRSwNP comorbidity as a reliable biomarker of asthma severity. Moreover, this study confirms the relevant role of type 2 inflammation, mainly concerning the eosinophilic component, in characterizing the asthma-CRS phenotype. Eosinophilic inflammation is in fact a shared pathogenic mechanism by both asthma and CRSwNP.

This study has some limitations, including the cross-sectional design, lack of mediators' assessment, evaluation of peripheral eosinophils alone, and missing data for some patients. Another selection bias was the recruitment of patients based on asthma visits at the tertiary level (subspecialist clinic), thus mostly including patients with persistent asthma. Nonetheless, this study was performed in a real-world setting. Increasing attention must be paid to the real-world studies because they may provide information more adherent to the daily practice, whereas randomized controlled trials involving selected patient populations may rarely mirror the real situation.^{37,38}

In conclusion, this study confirmed that CRS is a frequent asthma comorbidity because it affects more than one-third of outpatients with asthma. CRSwNP is associated with type 2 inflammation, mainly concerning blood eosinophil count of more than 300 cells/ μ L. These outcomes underline that the CRSwNP-asthma phenotype deserves adequate attention to careful management and optimal identification of the best-tailored therapy. In this regard, an appropriate therapy could, at present, include the potential beneficial treatment with a biologic that will benefit these 2 associated conditions, such as dupilumab, as very recently pointed out.^{39,40}

References

- Hastan D, Fokkens WJ, Bachert C, et al. Chronic rhinosinusitis in Europe—an underestimated disease. A GA²LEN study. *Allergy*. 2011;66(9):1216–1223.
- 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):1431–1440.
- 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.
- Orlandi RR, Kingdom TT, Hwang PH, et al. International consensus statement on allergy and rhinology: rhinosinusitis. *Int Forum Allergy Rhinol*. 2016;6(suppl 1):S22–S209.
- Lund VJ, Mackay IS. Staging in rhinosinusitis. *Rhinology*. 1993;31(4):183–184.
- Bachert C, Vignola AM, Gevaert P, Leynaert B, Van Cauwenberge P, Bousquet J. Allergic rhinitis, rhinosinusitis, and asthma: one airway disease. *Immunol Allergy Clin North Am*. 2004;24(1):19–43.
- Lin DC, Chandra RK, Tan BK, et al. Association between severity of asthma and degree of chronic rhinosinusitis. *Am J Rhinol Allergy*. 2011;25(4):205–208.
- Bachert C, Gevaert P, Holtappels G, Johansson SG, van Cauwenberge P. Total and specific IgE in nasal polyps is related to local eosinophilic inflammation. *J Allergy Clin Immunol*. 2001;107(4):607–614.
- Mygind N, Dahl R, Bachert C. Nasal polyposis, eosinophil dominated inflammation, and allergy. *Thorax*. 2000;55(suppl 2):S79–S83.
- Gevaert P, Bachert C, Holtappels G, et al. Enhanced soluble interleukin-5 receptor alpha expression in nasal polyposis. *Allergy*. 2003;58(5):371–379.
- Patou J, Holtappels G, Affleck K, et al. Enhanced release of IgE-dependent early phase mediators from nasal polyp tissue. *J Inflamm (Lond)*. 2009;6:11.
- Timmerman L. What's in a name? A lot, when it comes to 'precision medicine'. *Xconomy*. Available at: <https://xconomy.com/national/2013/02/04/whats-in-a-name-a-lot-when-it-comes-to-precision-medicine/>. Accessed November 14, 2019.
- Kaur R, Chupp G. Phenotypes and endotypes of adult asthma: moving toward precision medicine. *J Allergy Clin Immunol*. 2019;144(1):1–12.
- Guilleminault L, Oukel H, Belleguic C, et al. Personalised medicine in asthma: from curative to preventive medicine. *Eur Respir Rev*. 2017;26(143):160010.
- Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. GINA Guidelines. Available at: <http://www.ginasthma.org/>. Accessed November 6, 2019.
- Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319–338.
- Dweik RA, Boggs PB, Erzurum SC, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FeNO) for clinical applications. *Am J Respir Crit Care Med*. 2011;184(5):602–615.
- Nathan RA, Sorkness CA, Kosinski M, et al. Development of the Asthma Control Test: a survey for assessing asthma control. *J Allergy Clin Immunol*. 2004;113(1):59–65.
- Fasce L, Tosca MA, Olcese R, Milanese M, Erba D, Ciprandi G. The natural history of allergy: the development of new sensitizations in asthmatic children. *Immunol Lett*. 2004;93(1):45–50.
- Froidure A, Mouthuy J, Durham SR, Chanez P, Sibille Y, Pilette C. Asthma phenotypes and IgE responses. *Eur Respir J*. 2016;47(1):304–319.
- Zervas E, Samitas K, Papaioannu AI, Bakakos P, Loukides S, Gaga M. An algorithmic approach for the treatment of severe uncontrolled asthma. *ERJ Open Res*. 2018;4(1):00125–02017.
- GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Respir Med*. 2017;5:691–706.
- Ciprandi G, Cirillo I. The lower airway pathology of rhinitis. *J Allergy Clin Immunol*. 2006;118(5):1105–1109.
- Tay TR, Hew M. Comorbid “treatable traits” in difficult asthma: current evidence and clinical evaluation. *Allergy*. 2018;73(7):1369–1382.
- Oyinlola JO, Campbell J, Kousoulis AA. Is real-world evidence influencing practice? A systematic review of CPRD research in NICE guidances. *BMC Health Serv Res*. 2016;16:299.
- Shaw DE, Sousa AR, Fowles SJ, et al. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. *Eur Respir J*. 2015;46(5):1308–1321.
- Fleming L, Heaney L. Severe asthma—perspectives from adult and pediatric pulmonology. *Front Pediatr*. 2019;7:389.
- Southworth T, Pattwell C, Khan N, et al. Increased type 2 inflammation post rhinovirus infection in patients with moderate asthma. *Cytokine*. 2020;125:154857.
- Kalinauskaitė-Zukauske V, Januskevicius A, Janulaityte I, Miliauskas S, Malakauskas K. Expression of eosinophil β chain-signaling cytokines receptors, outer-membrane integrins, and type 2 inflammation biomarkers in severe non-allergic eosinophilic asthma. *BMC Pulm Med*. 2019;19(1):158.
- Edris A, De Feyter S, Maes T, Joos G, Lahousse L. Monoclonal antibodies in type 2 asthma: a systematic review and network meta-analysis. *Respir Res*. 2019;20(1):179.
- Denlinger LC, Phillips BR, Ramratnam S, et al. Inflammatory and comorbid features of patients with severe asthma and frequent exacerbations. *Am J Respir Crit Care Med*. 2017;195(3):302–313.
- Ricciardolo FLM, Sorbello V, Folino A, et al. Identification of IL-17F/frequent exacerbator endotype in asthma. *J Allergy Clin Immunol*. 2017;140(2):395–406.
- Avdeeva K, Fokkens W. Precision medicine in chronic rhinosinusitis with nasal polyps. *Curr Allergy Asthma Rep*. 2018;18(4):25.

34. Ren L, Zhang N, Zhang L, Bachert C. Biologics for the treatment of chronic rhinosinusitis with nasal polyps - state of the art. *World Allergy Organ J.* 2019; 12(8):100050.
35. Vlastos I, Gkouskou K, Doulaptsi M, Karatzanis A, Prokopakis EP. Precision medicine in rhinosinusitis. *Curr Allergy Asthma Rep.* 2019;19(2):12.
36. Price D, Wilson AM, Chisholm A, et al. Predicting frequent asthma exacerbations using blood eosinophil count and other patient data routinely available in clinical practice. *J Asthma Allergy.* 2016;9:1–12.
37. U.S. Food and Drug Administration. *Use of real-world evidence to support regulatory decision-making for medical devices. Guidance for industry and Food and Drug Administration. Staff document issued on August 31, 2017.* Bethesda: US Food and Drug Administration, US Department of Health and Human Services, Center for Devices and Radiological Health, Center for Biologics Evaluation and Research; 2017.
38. Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-world evidence - what is it and what can it tell us? *N Engl J Med.* 2016;375(23):2293–2297.
39. Le Floch A, Allinne J, Nagashima K, et al. Dual blockade of IL-4 and IL-13 with dupilumab, an IL-4R α antibody, is required to broadly inhibit type 2 inflammation [e-pub ahead of print]. *Allergy.* <https://doi.org/10.1111/all.14151>, Accessed December 31, 2019.
40. Iqbal IZ, Shih-Teng Kao S, Ooi EH. The role of biologics in chronic rhinosinusitis: a systematic review. *Int Forum Allergy Rhinol.* 2020;10(2):165–174.