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ORIGINAL ARTICLE

Eosinophilia, asthma, NERD and the use of oral corticosteroids predict uncontrolled chronic rhinosinusitis with nasal polyps after surgery

Elina Penttilä,[1,2] Saara Sillanpää,[3] Seija I Vento,[4] Jyri Myller,[5] Anni Koskinen,[4] Sari Hammarén-Malmi,[4] Anu Laulajainen-Hongisto,[4] Maija Hytönen,[4] Annina Lyly,[4,6] Markus Lilja,[4] Paula Kauppi,[6,7] Jura Numminen,[3] Markus Rautiainen,[3] Johanna Sahlman,[1] Mikko Nuutinen,[8] Sanna Toppila-Salmi,[6,8] Paula Virkkula[4,6]**

Abstract

Background: Severe uncontrolled chronic rhinosinusitis with nasal polyps (CRSwNP) is a challenging condition to treat. The European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS2020) has the following criteria when considering biological therapy for severe uncontrolled CRSwNP: eosinophilia, need for oral corticosteroids (OCS), symptom score, loss of sense of smell and co-morbid asthma.

Objective: This study aimed at finding associations of baseline factors with uncontrolled CRSwNP after endoscopic sinus surgery (ESS).

Methods: Electronic health record data of CRSwNP patients (N = 137) undergoing ESS in 2002–17 were used. Endpoints of uncontrolled CRSwNP were revision ESS, purchased OCS and antibiotic courses during follow up. Baseline factors were chosen based on EPOS2020 and the data available: nasal polyp (NP) eosinophilia, peripheral blood eosinophilia, co-existing asthma and/or non-steroidal anti-inflammatory drug exacerbated respiratory disease (NERD), need for OCS during the previous year, previous ESS, endoscopic NP score, and Lund-Mackay score of sinus computed tomography scans.

Results: During the follow-up of 10.1 ± 3.1 (mean ± standard deviation) years, 35 (25.5%) individuals underwent revision ESS. The best predictive model was obtained by a sum of baseline (1) blood eosinophilia ≥ 250 cells/µl and/or NP eosinophilia ≥ 30% (Eos), (2) asthma/NERD, and (3) ≥ 1 OCS/year. It was significantly associated with revision ESS, purchased doctor-prescribed OCS and antibiotic courses during follow-up.

Conclusion: We identified similar predictive variables for uncontrolled CRSwNP that are used in the EPOS2020 indications of biological therapy, thus suggesting that these estimates are usable in clinical practice.

Key words: asthma, chronic rhinosinusitis, computed tomography, eosinophilia, nasal polyp, sinusitis

From:
[1] Department of Otorhinolaryngology, Kuopio University Hospital, Kuopio, Finland
[2] University of Eastern Finland, Kuopio, Finland
[3] Department of Otorhinolaryngology – Head and Neck Surgery, Faculty of Medicine and Health Technology, Tampere University and Tampere University Hospital, Tampere, Finland
[4] University Hospital, Helsinki, Finland
[5] Department of Otorhinolaryngology, Päijät-Häme Central Hospital, Lahti, Finland
[6] Skin and Allergy Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
[7] Department of Pulmonary Diseases, Heart and Lung Center, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
[8] Haartman Institute, University of Helsinki, Helsinki, Finland

*shared last author

Corresponding author:
Elina Penttilä
Department of Otorhinolaryngology, Kuopio University Hospital
PO Box 1777 FI-70211 Kuopio, Finland
E-mail: elina.penttila@kuh.fi

Abbreviations:

AR	allergic rhinitis
ASA	acetylsalicylic acid
AUROC	area under the receiver operating characteristic curve
CRS	chronic rhinosinusitis
CRSwNP	chronic rhinosinusitis with nasal polyps
CT	computed tomography
Eos	blood eosinophilia ≥ 250 cells/µl and/or NP eosinophilia ≥ 30%

Abbreviations (Continued):

EPOS2020	European position paper on rhinosinusitis and nasal polyps 2020
ESS	endoscopic sinus surgery
LM	Lund-Mackay
NP	nasal polyp
MWU	Mann Whitney U test
NERD	NSAID-exacerbated respiratory disease
NSAID	non-steroidal anti-inflammatory drug
OCS	oral corticosteroid(s)
SD	standard deviation

Introduction

Chronic rhinosinusitis (CRS) is one of the most common chronic adult health problems with a prevalence ranging between 6–11%.[1,2] The impact of CRS on costs[3] and quality of life (QOL) is significant; analogous with asthma, chronic obstructive pulmonary disease and diabetes.[2] Its main phenotypes, CRS with nasal polyps (CRSwNP) and without (CRSsNP), differ in aetiologies, pathomechanisms and types of inflammation.[2,4,5] The prevalence of CRSwNP is 1–4%.[2] In CRSwNP patients, the prevalence of co-morbid asthma is about 45% and that of non-steroidal anti-inflammatory drug (NSAID) -exacerbated respiratory disease (NERD) is 8–26%.[2] These patients usually have eosinophilic hyperplastic inflammation on the airway mucosa and poor QOL.[2]

According to the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS2020), the definition of uncontrolled CRS is based on symptoms (obstruction, rhinorrhea/postnasal drip, facial pain/pressure, smell, sleep/fatigue), endoscopic findings of diseased mucosa, and need for rescue treatment.[2] The prevalence of uncontrolled CRS is 30–44% after appropriate guideline-based care.[2,6,7] Endoscopic sinus surgery (ESS) is considered after failure of baseline therapy. CRSwNP and CRSsNP patients have shown to benefit from ESS equally, although part of CRSwNP patients have polyp regrowth and need for revision ESS as signs of uncontrolled disease.[6,8-10] Revision ESS has shown to be associated with sex, younger age, nasal polyps (NPs) or blood eosinophilia, smoking, allergic rhinitis (AR), previous sinus surgery, occupational exposure, presence of NPs, need for systemic medication, asthma and NERD.[7,11-17] EPOS2020-based criteria for severe uncontrolled CRSwNP, in which biological therapy could be considered, are high eosinophilia, need for oral corticosteroids (OCS), symptom score, loss of sense of smell and co-morbid asthma.[2]

Early detection and prevention of severe uncontrolled CRSwNP is important in order to decrease the morbidity and costs.[18,19] Identification of biomarkers and predictive factors is important to help hit the uncontrolled CRSwNP cases early. Yet, only limited knowledge of the putative risk factors behind uncontrolled CRSwNP exists.

This study aimed at finding associations of baseline factors with uncontrolled CRSwNP after surgery. We hypothesized that models related to a history of rescue therapy, eosinophilia and co-morbidities are significantly associated with uncontrolled CRSwNP.

Methods

Setting

A retrospective hospital-based sample of CRSwNP patients after surgery.

Subjects

This retrospective follow-up study was carried out of the CRSwNP patients visiting Departments of Otorhinolaryngology at Tampere, Kuopio and Helsinki University Hospitals, and Päijät-Häme Hospital between 2002 and 2017. The study (nro 31/13/03/00/2015) was approved by the ethical committee of the Hospital Districts, an approval was obtained that there was no need for written informed consent for this retrospective follow-up study.

The inclusion criterion was ESS within 1 year after the baseline consultation and this procedure was defined as the "baseline ESS". Previous sinonasal surgery was allowed. The exclusion criteria were age ≤ 16 years, no patient record information of endoscopic NPs during baseline visit or baseline ESS, missing data of baseline operation or follow-up, biological therapy for asthma, acetylsalicylic acid desensitization, eosinophilic granulomatosis with polyangiitis, primary ciliary dyskinesia, cystic fibrosis, acute fungal rhinosinusitis, or severe systemic disease such as active cancer. CRSwNP was diagnosed according to the EPOS2020.[2] Data was available of 137 CRSwNP patients fulfilling the above inclusion/exclusion criteria. These data were obtained from (i) a random sample of 92 CRSwNP patients who had undergone ESS consultation between 2002-2017 at Helsinki/Tampere/Kuopio University Hospital and Päijät-Häme Central Hospital; (ii) a random sample of 29 CRSwNP patients who had undergone nasal polyp biopsy during ESS consultation/ESS between 2005-2007 at Tampere University Hospital; (iii) a random sample of 16 CRSwNP cases who had undergone ESS consultation between 2006-2011 at Tampere University Hospital.

Outcomes

The data of all variables were obtained from electronic health records. The mean (±SD) total follow-up time was 10.1 (±3.1) years. The following markers of uncontrolled CRSwNP were assessed: (1) time until revision ESS (if any); the time to the end of follow-up (until January 2019), (2) the number of purchased doctor-prescribed antibiotic courses/year, (3) the number of purchased doctor-prescribed oral corticosteroid (OCS) courses/year defined as 0 or ≥ 1, and/or continuous OCS due to exacerbation of CRSwNP and/or asthma. The search for prescription data of the last two years was performed from the nation-wide electronic prescription database during 2016–2020, at least 3 years apart from the baseline ESS.

Factors

The seven variables of interest were

- baseline NP tissue eosinophilia ≥ 30% and/or peripheral blood eosinophilia ≥ 250 cells/μl during the time of baseline visit ±3 years (no/missing, yes)[2,20]
- a history of ≥ 1 OCS course or continuous OCS during the past year (no/missing, yes)[2,20]

- a history of ≥ 1 previous ESS (no/missing, yes)[21]
- Lund-Mackay (LM) score ≥ 14/24 of baseline sinus CT scans (no/missing, yes)[20]
- baseline endoscopic NP score ≥ 5/8[20]
- In addition, the following factors were added in the survival/logistic regression models: female sex, allergic rhinitis (AR), current smoking, history of ≥ 4 antibiotic courses/year.

The diagnoses of co-existing diseases were based on self-reported doctor diagnosed and/or patient record document confirmation of a doctor-diagnosed disease. A doctor-diagnosed asthma fulfills the definition of Finnish national drug reimbursement right: typical history, clinical features, at least one of the following physiologic criteria: (i) a variation of 20% or greater in diurnal peak expiratory flow (PEF) recording (reference to maximal value); (ii) an increase of 15% or greater in PEF or forced expiratory volume in 1 second (FEV1) with b-agonist; or (iii) an decrease of 15% or greater in PEF or FEV1 in exercise testing. The NERD diagnosis was based on a positive history of wheeze/cough or naso-ocular symptoms after intake of NSAID.

Statistics

Statistical analysis was carried out by the SPSS Base 15.0 Statistical Software Package (SPSS Inc., Chicago, IL, USA). Receiver operating characteristic (ROC) analysis was used to identify cut-off point(s) at which a variable predicts the outcomes: revision-ESS, purchased OCS and antibiotic -courses during the follow-up. The area under the curve (AUC) was used to obtain a probability of models that an individual will have uncontrolled CRSwNP after surgery. AUC of 0.5 suggests no discrimination, AUC over 0.5 but less than 0.7 is considered poor, AUC over 0.7 is considered acceptable, AUC over 0.8 is considered excellent, and AUC over 0.9 is considered outstanding. The best predictor model (statistically significant AUC ≥ 0.75, for all the three outcomes), was the sum model of baseline Eos + asthma/NERD + OCS (1 point for each risk factor), in which Eos = nasal polyp (NP) eosinophilia ≥ 30% and/or blood eosinophilia ≥ 250 cells/µl; Asthma/NERD = asthma and/or NERD; OCS = history of ≥ 1 course(s) OCS during the past year. This sum model of baseline Eos + asthma/NERD + OCS predictor was entered into survival analysis with Logrank test (revision ESS-rate) and comparative analysis (purchased OCS/antibiotic courses). Cox´s proportional hazards model was used to examine the association of factors with the time until revision ESS in the follow-up. Logistic regression models were used to examine the association of factors with purchased OCS or antibiotic courses in the follow-up. The results are reported as hazard ratios (HR) or odds ratios (OR) with 95% confidence intervals. An interaction term was added in the regression models to test interactions berween variables. Associations were assessed by the Fisher's exact test (dichotomous) and differences in medians were studied by Kruskal-Wallis and Mann Whitney U test (continuous). Two-tailed *p*-values of < 0.05 were considered statistically significant.

Sample size calculation was performed with a ratio between uncontrolled to controlled CRSwNP 1:2[22] with an accrual interval of 15 years, additional follow-up of 3 years and the mean follow-up of 10 years. In survival models 126 patients were needed to reject the null hypothesis with power 80% and $p = 0.05$. For validation, we used a population of 172 CRSwNP patients having ESS ≤ 12 months after baseline visit, which was obtained from Helsinki University Hospital registry data of a random sample of 5080 rhinitis and rhinosinusitis patients in 2005-19. The data were collected by using information extraction and data processing packages of electronic patient records. The variables of interest were eosinophilia (no/missing, yes); asthma/NERD (no/missing, yes); a history of OCS (no/missing, yes), during the first 3 years after the baseline visit. Cox's proportional hazards model was used to validate the association of the sum model of baseline Eos + Asthma/NERD + OCS (1 point per each; values 0-3) with the time until revision ESS in this population.

Results

Patient characteristics

Of the total of 137 patients, 57 (41.6%) were female, 51 (37.2%) had patient recorded history of AR, 59 (43.1%) had asthma, 17 (12.4%) had NERD, and 25 (18.2%) were current smokers. At the baseline, the age (mean ± SD) was 48.1 ± 14.8 years. Forty-seven (34.3%) patients did not have a patient-record history of previous CRS-operation(s). Thirty-five patients (25.5%) underwent revision ESS, which was performed (mean ± SD) 3.4 ± 2.8 years after the baseline surgery. Of these, twenty-seven (77.1%) underwent one and eight (22.9%) patients underwent two revision surgeries during the follow-up. Revision ESS was significantly associated with young age, baseline NP eosinophilia ≥ 30%, and with a positive history of previous OCS (**Table 1**). The mean (±SD) total follow-up time was 10.1 (±3.1) years and, the follow-up time until the first event (revision ESS/death/Jan2019) was 8.0 (±4.0) years.

Table 1. Patient history data of the study subject groups who did or did not undergo revision endoscopic sinus surgery (ESS) during the follow-up.

Baseline factors	No revision ESS n = 102	Revision ESS n = 35	p
Personal characteristics			
Female, n (%)	39 (38.2)	18 (51.4)	.23
Age, mean (±SD)	49.7 (14.5)	41.3 (11.8)	**.003**
Follow-up time, mean (±SD)	10.1 (3.1)	10.0 (3.2)	.85

Table 1. (Continued)

Baseline factors	No revision ESS n = 102	Revision ESS n = 35	p
Lifestyle factors			
Current smoking, n (%)	18 (24.0)	7 (21.9)	1.00
Co-existing diseases			
Allergic rhinitis, n (%)	34 (35.8)	17 (54.8)	.091
Asthma, n (%)	39 (40.6)	20 (60.6)	.068
NERD, n (%)	10 (10.3)	7 (22.6)	.12
Disease characteristics			
Radiologic LM score, mean (±SD)	13.7 (4.1)	15.4 (5.1)	.064
Endoscopic NP score ≥ 5/8, n (%)	28 (27.5)	9 (25.7)	1.00
NP eosinophilia1 ≥ 30 %, n (%)	19 (34.5)	15 (68.2)	**.011**
Blood eosinophilia ≥ 250 cells/µl, n (%)	23 (54.8)	13 (76.5)	.15
Operation/exacerbation history			
≥ 1 previous ESS, n (%)	33 (32.4)	14 (40.0)	.54
≥ 4 antibiotic courses/year, n (%)	12 (22.6)	7 (41.2)	.21
≥ 1 OCS course(s)/year, n (%)	20 (19.6)	13 (37.1)	**.042**

NERD = patient-reported non-steroidal anti-inflammatory drug -exacerbated respiratory disease; OCS = oral corticosteroid(s). *P* values by Fisher´s exact test (dichotomous variables) or Mann Whitney U test (continuous variables). SD = standard deviation.

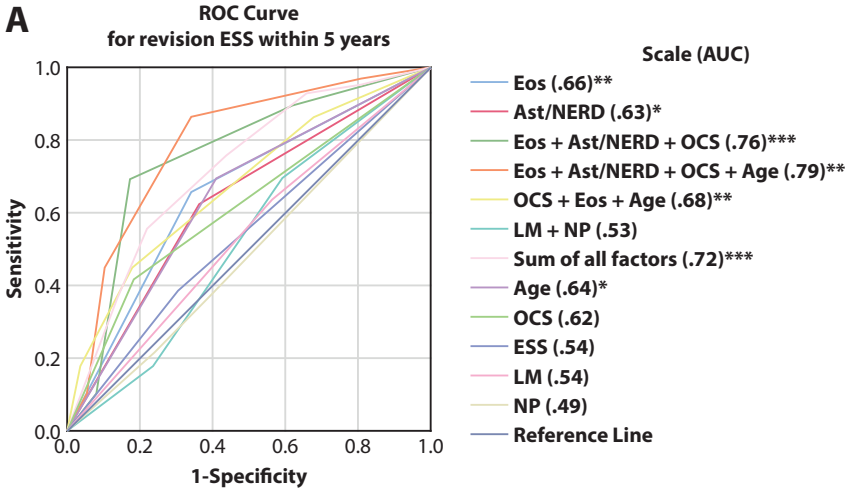

Figure 1. The Receiver operating characteristic (ROC) curve plots for predictor models of baseline factors. Area under the ROC curve (AUC) was used to obtain a probability of a model that an individual will have uncontrolled chronic rhinosinusitis with nasal polyps (CRSwNP) after surgery. Three outcome measurements of uncontrolled CRSwNP were used: (A.) revision-endoscopic sinus surgery (ESS) within 5 years, (B.) purchased ≥ 1 oral corticosteroid (OCS) course(s)/year continuous OCS during the follow-up, (C.) purchased > 2 antibiotic courses/year during the follow-up. The number of subjects was 130 in each curve. (A.) Seven non-revised cases were excluded from analysis due to a follow up of ≤ 5 years. (B.-C.) Electronic prescription data was not available of 7/137 cases. The scale of predictor models are the same in all frames (A.-C.). Seven baseline factors were used in the predictor models: Eos = nasal polyp (NP) eosinophilia ≥ 30% and/or blood eosinophilia ≥ 250 cells/µl; Ast/NERD = asthma and/or non-steroidal anti-inflammatory drug -exacerbated respiratory disease; OCS = history of ≥ 1 OCS during the past year; Age = age < 45 years; ESS = a history of ≥ 1 ESS; LM = Lund-Mackay (LM) score ≥ 14/24; NP = endoscopic nasal polyp (NP) score ≥ 5/8. + indicates the sum models (1 point per each factor). Significant *p* values *< 0.05, **< 0.01, ***< 0.001.

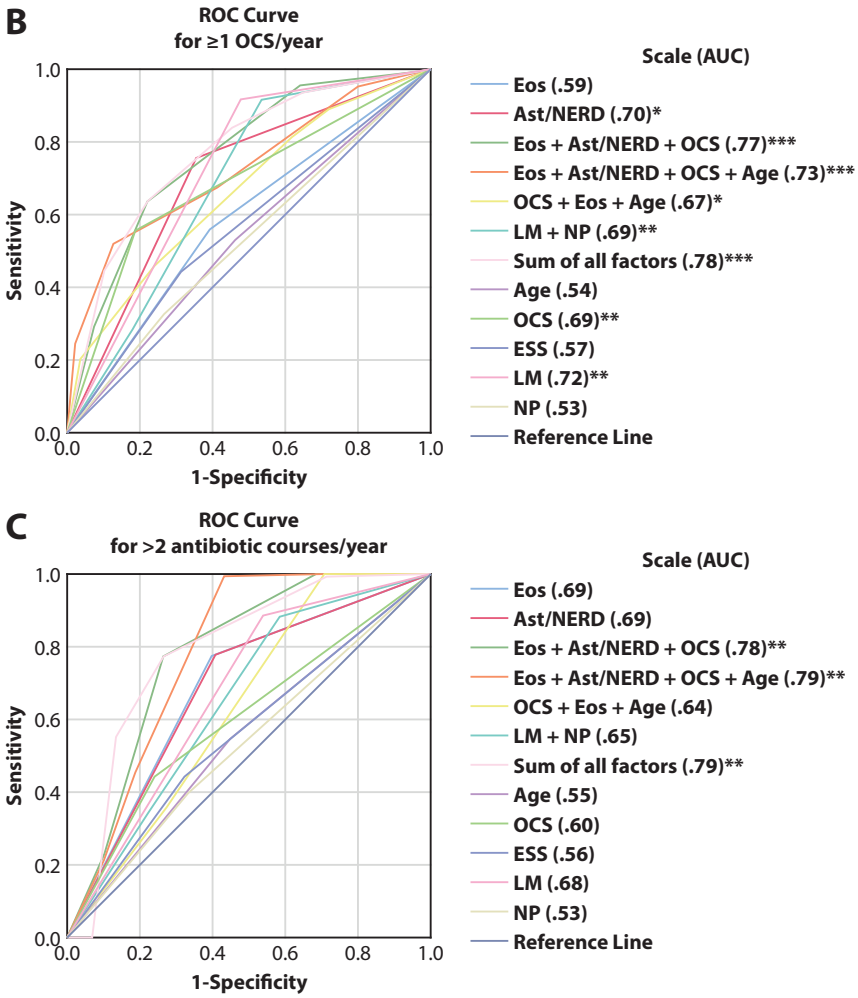

Figure 1. (Continued)

ROC analyses of predictor models

Cut-off values of continuous variables were identified by ROC analysis (data nor shown). AUC was used to obtain a probability of model that an individual will have uncontrolled CRSwNP after surgery, which was measured by revision-ESS (**Figure 1A**), purchased OCS (**Figure 1B**) and antibiotic courses (**Figure 1C**) during the follow-up. The best predictor model for all the three outcomes was the sum model of baseline Eos + asthma/NERD + OCS (1 point for each risk factor, AUC > 0.75, $p < 0.01$; **Figure 1 A-C**), in which Eos = nasal polyp (NP) eosinophilia ≥ 30% and/or blood eosinophilia ≥ 250 cells/μl; Asthma/NERD = asthma and/or NERD; OCS = history of ≥ 1 course(s) OCS during the past year. The second-best predictor model was the sum of baseline Eos + Asthma/NERD + OCS +Age (AUC > 0.72, $p < 0.01$; **Figure 1 A-C**), in which Age = age < 45 years. The third-best predictor model was the sum of all the seven baseline factors (AUC > 0.71, $p < 0.01$; **Figure 1 A-C**). Of individual predictors, baseline eosinophilia had the second-best and age had the third-best predictive potential of uncontrolled CRSwNP after surgery, yet their AUC values (varying between 50-70) were generally lower than that of the sum model Eos + Asthma/NERD + OCS (**Figure 1 A-C**).

Predictors of revision ESS

The sum model baseline Eos + Asthma/NERD + OCS (1 point of each; total range 0-3 points; values 0-1, 2-3) was used to predict the time until revision ESS. High value (2-3 points) was significantly associated with revision ESS during the follow-up ($p < 0.001$, **Figure 2A**).

Cox´s proportional hazards model was used to investigate the association between the survival time until the revision ESS, and the baseline factors. In univariate model, revision ESS was statistically significantly associated with young age, asthma/NERD, baseline eosinophilia and a positive history of OCS ($p < 0.05$, **Table 2**). When entering the significant predictors into a multivariable model, revision ESS was statistically significantly associated with young age, asthma/NERD and baseline eosinophilia, but not with OCS (**Table 2**). When adding the interaction term in this model there was a significant interaction between eosinophilia and history of OCS (adjusted OR [CI95%] was 0.41 [0.03-0.62]), $p = 0.009$ (**Table 2**).

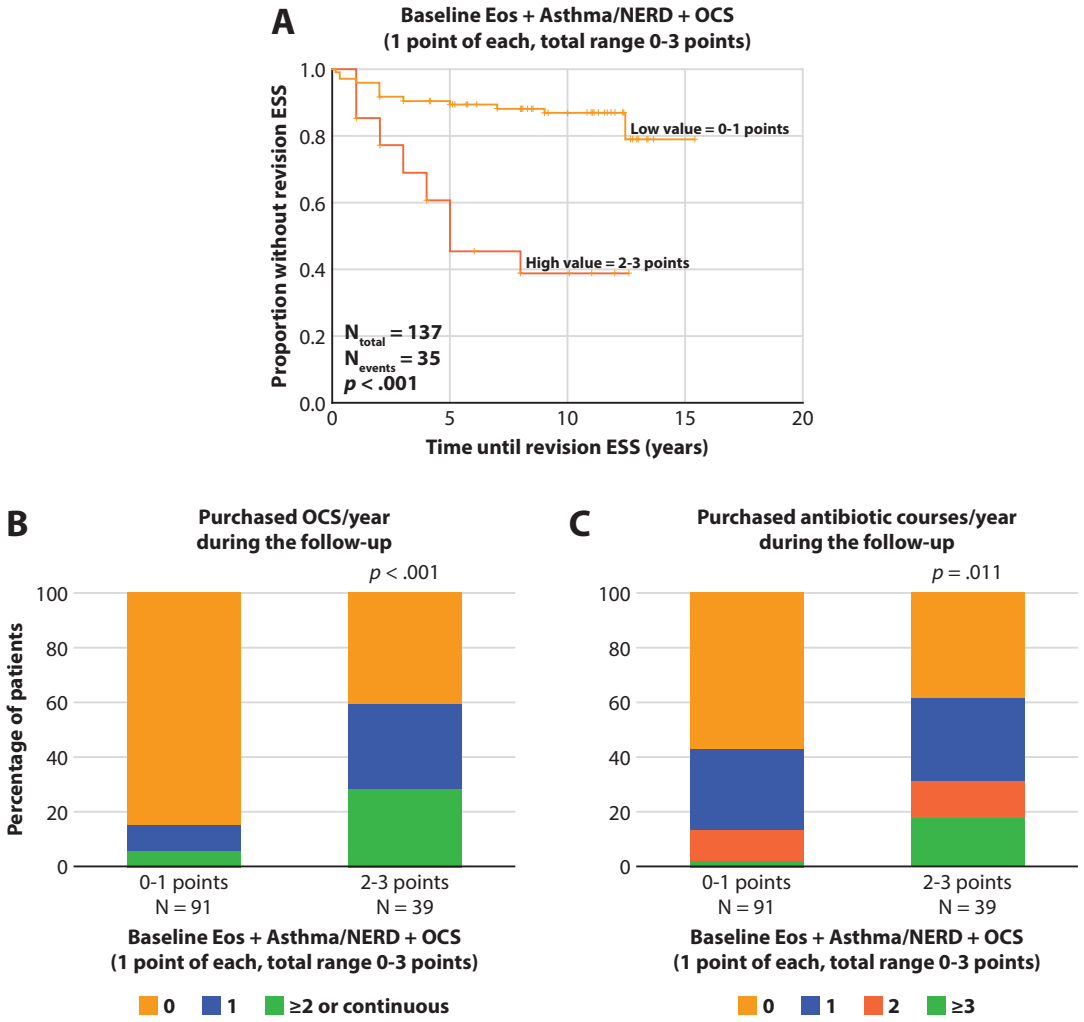

Figure 2. (A.) Predictive effect of sum model of baseline Eos + Asthma/NERD + OCS (1 point per each; values 0-3) to the time until revision endoscopic sinus surgery (ESS), according to the Kaplan-Meier method. OCS = history of ≥ 1 oral corticosteroid course(s) during the past year;
Eos = baseline nasal polyp eosinophilia ≥ 30% and/or baseline blood eosinophilia ≥ 250 cell/µl;
Asthma/NERD = patient reported-doctor diagnosed asthma and/or NSAID exacerbated respiratory disease (NERD). *P*-values by log rank test. (B-C.) Comparison of the number of purchased doctor-prescribed (A.) oral corticosteroid (OCS) course(s)/year (B.) antibiotic course(s)/year during the follow-up in the two patient groups: having low or high sum points of baseline Eos + Asthma/NERD + OCS (1 point per each; values 0-3). OCS = history of ≥ 1 oral corticosteroid course(s) during the past year; Eos = baseline nasal polyp eosinophilia ≥ 30% and/or baseline blood eosinophilia ≥ 250 cell/µl; Asthma/NERD = patient reported-doctor diagnosed asthma and/or NSAID exacerbated respiratory disease (NERD). The follow-up OCS were prescribed due to exacerbation of CRSwNP and/or asthma. Five patients were using continuous OCS. The search for prescription data was performed from Nation-wide electronic prescription database during 2016-20. The mean (±SD) total follow-up time was 10.1 (±3.1) years. P-value by Fisher´s exact test. Electronic prescription data was not available of 7/137 cases.

Table 2. Unadjusted and adjusted Cox´s proportional hazard models for the baseline factors analyzed fitted for the need for follow-up surgery until the first follow-up surgery.

Baseline factors	Events	Univariate			Multivariable		
		HR	95% CI	*p* value	HR	95% CI	*p* value
Gender							
Male	17	1					
Female	18	1.51	0.78-2.93	.22	Not entered		
Age		.97	0.95-0.99	**.009**	0.97	0.95-0.99	**.015**

Table 2. (Continued)

Baseline factors	Events	Univariate			Multivariable		
		HR	95% CI	*p* value	HR	95% CI	*p* value
Current smokers							
No	25	1					
Yes	7	0.87	0.37-2.00	.73	Not entered		
Allergic rhinitis							
No	14	1					
Yes	17	1.98	0.98-4.02	.058	Not entered		
Asthma and/or NERD							
No	14	1			1		
Yes	21	2.29	1.16-4.51	**.017**	2.20	1.07-4.51	**.032**
Radiologic LM score							
1-15	13	1					
16-24	22	1.44	0.72-2.85	.30	Not entered		
NP score[2]							
1-4	26	1					
5-8	9	0.94	0.44-2.01	.87	Not entered		
NP eos ≥ 30% or Blood eos ≥ 250 cells/µl							
No	12	1			1		
Yes, either or both	23	3.13	1.55-6.30	**.001**	2.32	1.10-4.90	**.028**
Number of previous ESS							
0	21	1					
≥ 1	14	1.37	0.70-2.70	.36	Not entered		
≥ 4 antibiotic courses/year							
No	10	1					
Yes	7	2.13	0.81-5.61	.12	Not entered		
≥ 1 OCS course(s)/year							
No	18	1			1		
Yes	17	2.34	1.17-4.68	**.016**	1.42	0.66-3.03	0.37

All 137 CRSwNP patients underwent baseline ESS within 1 year after the baseline consultation. The number of events, e.g. patients who underwent revision ESS during follow-up was 35. The mean (±SD) follow-up time until the first event (revision ESS/death/Jan2019) was 8.0 (±4.0) years. The mean (±SD) total follow-up time was 10.1 (±3.1) years. NERD = patient-reported non-steroidal anti-inflammatory drug -exacerbated respiratory disease; AR = allergic rhinitis; OCS = oral corticosteroid(s), NP = nasal polyp, eos = eosinophils. Only the variables that had significant *p* values (< 0.05, marked in bold) in univariate model were entered into the multivariable model. When adding the interaction term in the revision-free survival model there was a significant interaction between eosinophilia and a history of OCS (adjusted OR [CI95%] was 0.14 [0.03-0.62]), $p = 0.009$).

Predictors associating with follow-up OCS

The association between the baseline sum model Eos + Asthma/NERD + OCS and the number of purchased doctor-prescribed OCS course(s)/year during the follow-up was studied. The number of purchased OCS was significantly higher in the patient group who had high value (1-2 points) of baseline Eos + asthma/NERD + OCS, as compared with the patient group who had low value (0-1 points) of Eos + Asthma/NERD + OCS ($p < 0.001$, **Figure 2B**).

Logistic regression model was used to investigate the association between baseline factors and the outcome measurement "follow-up ≥ 1 OCS course(s)/year and/or continuous OCS", shortened here as "follow-up OCS". The follow-up OCS was significantly associated with asthma/NERD, high baseline LM CT score, and a positive history of OCS (**Table 3**). When entering these variables and gender and age into multivariable model the OR values were changed 22-73% but remained significant (**Table 3**). None of the subjects had started with biological therapy during the follow-up.

Table 3. Univariate and multivariable logistic regression models. The follow-up outcome was ≥ 1 purchased doctor-prescribed oral corticosteroid (OCS) course(s)/year or continuous OCS.

Baseline factors	Univariate			Multivariable		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Gender						
Male	1			1		
Female	1.44	0.60-3.46	.41	1.13	0.39-3.26	.82
Age	.99	0.96-1.03	.71	0.99	0.95-1.02	.42
Asthma and/or NERD						
No	1			1		
Yes	5.82	2.14-15.84	.001	4.49	1.46-13.80	**.009**
Radiologic LM score						
1-13	1			1		
14-24	12.65	2.84-56.40	.001	8.38	1.77-39.70	**.007**
≥ 1 OCS course(s)/year						
No	1			1		
Yes	5.76	2.27-14.64	< .001	3.62	1.28-10.20	**.015**

The follow-up OCS were prescribed due to exacerbation of CRSwNP and/or asthma. Five patients were using continuous OCS. The search for follow-up prescription data was performed from Nation-wide electronic prescription database during 2016-20. The mean (±SD) total follow-up time was 10.1 (±3.1) years. Electronic prescription data was not available of 7/137 cases. Only baseline factors that were significant ($p < 0.05$) in the association are shown, added by gender and age. No significant interaction was detected in adjusted logistic regression models between asthma/NERD, eosinophilia or OCS. NERD = patient-reported non-steroidal anti-inflammatory drug -exacerbated respiratory disease, LM = Lund-Mackay, OR = odds ratio, CI = confidence interval.

Table 4. Univariate and multivariable logistic regression models. The follow-up outcome was > 2 purchased doctor-prescribed antibiotic course (s).

Baseline factors	Univariate			Multivariable		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Gender						
Male	1			1		
Female	1.90	0.49-7.44	.36	1.23	0.29-5.29	.78
Age	.97	0.93-1.02	.24	0.97	0.92-1.02	.28
Asthma and/or NERD						
No	1			1		
Yes	5.14	1.03-25.80	**.047**	5.26	0.98-28.14	.052
NP eos ≥ 30% or Blood eos ≥ 250 cells/μl						
No	1			1		
Yes, either or both	5.32	1.06-26.71	**.042**	4.40	0.83-23.17	.081

The follow-up antibiotic courses were prescribed due to exacerbation of CRSwNP and/or asthma. The search for follow-up prescription data was performed from Nation-wide electronic prescription database during 2016-20. The mean (±SD) total follow-up time was 10.1 (±3.1) years. Electronic prescription data was not available of 7/137 cases. Only baseline factors that were significant ($p < 0.05$) in the association are shown, added by gender and age. No significant interaction was detected in adjusted logistic regression models between asthma/NERD, eosinophilia or OCS. NERD = patient-reported non-steroidal anti-inflammatory drug -exacerbated respiratory disease, NP = nasal polyp, eos= eosinophils, OR=odds ratio, CI= confidence interval.

Predictors associating with follow-up antibiotic courses

The association between the baseline sum model Eos + Asthma/NERD + OCS and the number of purchased doctor-prescribed antibiotic course(s)/year during the follow-up was studied. The number of purchased antibiotic courses was significantly higher in the patient group who had high value (1-2 points) of baseline Eos + Asthma/NERD + OCS, as compared with the patient group who had low value (0-1 points) of Eos + Asthma/NERD + OCS (p = .011, **Figure 2C**).

Logistic regression model was used to investigate the association between baseline factors and the outcome measurement "follow-up > 2 antibiotic course(s)/year", shortened here as "follow-up antibiotics". The use of follow-up antibiotics was significantly associated with asthma/NERD and baseline eosinophilia (Table 4). When entering these variables and gender and age into multivariable model the OR values changed 2–17% but were insignificant (**Table 4**).

Validation analyses

Validation analysis was performed from a data of 172 CRSwNP patients. Of these 45 (26.2%) underwent revision ESS at (mean ± SD) 36.95 ± 33.26 months after the baseline surgery. The sum model baseline Eos + Asthma/NERD + OCS (1 point of each; total range 0-3 points; values 0-1, 2-3) was used to predict the time until revision ESS. High value (2-3 points) was significantly associated with revision ESS during the follow-up (HR = 1.93, 95%CI 1.05-3.57, p = 0.035), when compared to the low value (0-1 points).

Discussion

This study was carried out to evaluate the association of baseline factors with uncontrolled CRSwNP after surgery. We found that a sum model of "eos + Asthma/NERD + OCS" had a good predictive potential for uncontrolled CRSwNP, as measured by revision-ESS, purchased OCS and antibiotic courses during the follow-up. EPOS2020 recommends using the following criteria when considering biological therapy for severe uncontrolled CRSwNP: eosinophilia, need for oral corticosteroids, symptom score, loss of sense of smell and co-morbid asthma.[2]

The present study showed that revision surgery was performed to a quarter of cases, which is in line with a population-based study that identified revision ESS in a fifth of CRSwNP patients.[23] Long-term follow-up studies on clinical cohorts in CRSwNP are rare. Two prospective studies have evaluated revision rates in 32 and 47 patients with 10 and 12 year follow-ups and reported 25% and 37% revision rates.[24,25] The present study showed that 43% had co-morbid asthma and 12% had NERD, which is in accordance with the previous literature,[2] showing that the prevalence of NERD is 10–16% in hospital-level CRSwNP patients.

Early prediction of disease control may help to adopt adequate measures to prevent prolonged uncontrolled disease. Of individual predictors, we found that asthma/NERD had the best predictive potential of uncontrolled CRSwNP after surgery, as measured by revision ESS and purchased OCS/antibiotics. This is in line with previous studies showing that asthma and NERD are common comorbidities of CRS and that the upper and lower airway diseases exacerbate each other.[2] Recalcitrant CRS increases incidence of asthma and endoscopic surgery of CRS has been reported to improve asthma control in up to 75% of patients.[2] Both asthma and NERD patients with CRSwNP benefit from ESS, but long-term recurrence seems more common with these comorbidities.[2] Among patients with co-morbid CRSwNP and asthma 96% had polyp recurrence during the 5-year follow-up, despite the type of extensive surgery.[26] It seems that CRSwNP patients with asthma and NERD would benefit from a customized treatment plan and follow-up beyond first surgery in order to achieve better long-term outcomes.

Of individual predictors, baseline eosinophilia had the second-best predictive potential for uncontrolled CRSwNP after surgery. Baseline eosinophilia was associated with revision ESS and purchased antibiotics in the follow-up, reflecting uncontrolled CRSwNP. This is in line with prior literature regarding the importance of eosinophilia as a predictor. Eosinophilic histology has been shown to be an important risk factor for revision ESS.[7,13,15,21,27] In addition to recurrence of polyps, mucosal eosinophilia in CRSwNP has been associated with more severe disease and anosmia.[13,15,27,28] In a recent study of CRSwNP patients with mucosal eosinophilia, the recurrence was as high as 48% in three year follow-up when using the EPOS 2012 criteria for uncontrolled CRS.[13,29] Blood eosinophilia has also shown to predict severe eosinophilic asthma and/or severe CRSwNP.[2,7]

Age had the third best predictive potential of individual predictors for uncontrolled CRSwNP after surgery. Young age was associated with revision ESS and purchased OCS in the follow-up. This is in line with a study in which young age was shown to be associated with revision surgery.[15] It is possible that with increasing age comorbidities, adaptation to symptoms or perhaps decreasing recurrence may influence both surgeon's and patient's decision on surgery, or the need for OCS. On the other hand, having a history of OCS was associated with the purchased OCS courses/continuous OCS in the follow-up, which could indicate persistence of uncontrolled inflammation in the airways. Our study group has previously shown among CRS patients, that baseline OCS predicted the need for follow-up ESS after baseline surgery.[16]

The present study showed that the sum model of eos + Asthma/NERD + OCS had better predictive potential than individual predictors, yet adding one or several variables (such as age) to the sum model did not improve the estimate of uncontrolled CRSwNP. Tao et al. have shown that tissue eosinophil ratio > 0.206 or blood eosinophil ratio > 0.025, LM score ≥ 15 and CT ethmoid score ≥ maxillary score were independent risk factors for uncontrolled CRSwNP.[7] The study group generated a pathological model (tissue eosinophil ratio and LM score) and a clinical model (blood eosinophil ratio, LM score and CT score) to categorize CRS into mild, moderate, and severe.[7] The study also demonstrated that tissue eosinophilia does not explain all uncontrolled CRS as nearly 50% of patients still had uncontrolled CRS with tissue eosinophilia under 21%. This is in line with our findings that baseline eosinophilia did not have a good predictive potential alone as compared to predictive model.

In addition to the studies using predictive models, high CT scores,[7] high preoperative endoscopic Lund-Kennedy scores for polyposis,[17] radiological inflammatory findings in frontal sinuses[30] and changes in Sino-Nasal Outcome Test -22 scores after surgery[2,14] have been shown to increase the risk of recurrence.

Due to the poorly defined criteria of revision surgery and the fact that not all uncontrolled patients will undergo surgery, merely prediction of revisions does not represent uncontrolled disease comprehensively. As an end point representing an uncontrolled disease, revisions should preferably be combined with other measures, such as health-related QOL or need for systemic medication, as in this study, to find the best predictors of uncontrolled disease.[14,31,32] Definitions and risk factors of uncontrolled CRS have been investigated and these studies have shown high prevalence of uncontrolled CRS.[2,6,7,29] EPOS 2012 and 2020 defined uncontrolled disease by combining symptoms, endoscopic findings and systemic medication use.[2,29] In a follow-up studies using these criteria at least 44% of patients were found uncontrolled and 37% of patients were found partly controlled at 3–5 years after ESS[6] and 30% uncontrolled and partly controlled 22%, after 29 months respectively.[7]

We acknowledge that data was not available to use EPOS-definition of uncontrolled CRSwNP in this study, including unavailable symptom/smell data and data of cutoff value of polyp eosinophilia > 10%, limiting thus the comparison of our findings with other studies. We acknowledge using cutoff value 30% of nasal polyp eosinophilia leaves possibility to miss some eosinophilic cases, who have lower tissue eosinophilia due to corticosteroids or other reasons. It was not possible to analyze different cutoff values, such as 10%,[33] as detailed data of eosinophilis and other leukocytes was lacking from most of the cases. We have previously detected that a cutoff value of about 30% eosinophilia predicts uncontrolled CRSwNP in our population.[20] Similar findings have been presented also in Asian populations.[34] Yet more studies by using several cutoff values are mandatory. Despite these limitations, the present study was able to identify similar predictive variables for uncontrolled CRSwNP that are used in the EPOS2020 indications of biological therapy, thus suggesting that these estimates are usable. Our analysis of revision surgery may have been influenced by several factors unrelated to recurrence of CRS, including wait-times for surgery, operative technique, and surgeons/patients' personal preferences. On the other hand, we were also able to replicate the efficacy of our results by using three different outcome measurements (revision ESS, purchased OCS/antibiotic courses), which could decrease the concerns of bias related to personal opinions. In addition, the survival analysis was validated in another CRSwNP population and the result remained similar. Despite the efforts in the definition of uncontrolled CRSwNP cases in this study, we acknowledge that some patients with recurrence undoubtedly sought treatment elsewhere. On the other hand, public medical care covers over 90% of operations in Finland,[35] and our data covered all patient record data of airway diseases (including asthma/allergy) of all public hospitals of the Hospital districts observed. Also, the patients finishing hospital follow-ups were still followed by electronic prescriptions of rescue treatment. A significant proportion of patients in this study were poorly controlled, which indicates that improved identification and targeted treatment of these patients is still needed in the future. Our research results support the EPOS severe disease criteria.

Conclusion

The sum model of eosinophilia, asthma/NERD and OCS had a good predictive potential for uncontrolled CRSwNP. These predictors are consistent with the EPOS2020 criteria.

Conflict of interest statement

The authors declare that there is no conflict of interest regarding this article.

Competing interests

STS reports consultancies for AstraZeneca, ERT, Novartis, Sanofi Pharma, and Roche Products and a grant of GSK, outside the submitted work. ALH reports a grant from Orion research foundation, outside the submitted work.

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Author contribution

ST-S planned the study, performed statistics with MN and, collected the data with EP, SS, MH, AK, SH-M, ALH, JN, JM, MR, and AL. PV, EP and ST-S wrote the manuscript. All authors critically commented the manuscript.

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