Factors Affecting the Control of Chronic Rhinosinusitis With Nasal Polyps: A Comparison in Patients With or Without NERD

Markus Jukka Lilja, MD, PhD[1,2] , **Anni Koskinen, MD, PhD**[1,2],
Paula Virkkula, MD, PhD[1,2] , **Seija Inkeri Vento, MD, PhD**[1],
Jyri Myller, MD, PhD[3], **Sari Hammarén-Malmi, MD, PhD**[1],
Anu Laulajainen-Hongisto, MD, PhD[1,2] ,
Maija Hytönen, MD, PhD[1], **Antti Mäkitie, MD, PhD**[1],
Jura Numminen, MD, PhD[4], **Saara Sillanpää, MD, PhD**[4],
Hannu Raitiola, MD, PhD[4], **Markus Rautiainen, MD, PhD**[4], and
Sanna Katriina Toppila-Salmi, MD, PhD[2,5]

Abstract

Objectives: The aim was to compare the control of chronic rhinosinusitis with nasal polyps (CRSwNP) after endoscopic sinus surgery (ESS), in patients with/without nonsteroidal anti-inflammatory drug exacerbated respiratory disease (NERD).
Study Desing: A retrospective hospital-based sample of CRSwNP patients with/without NERD with follow-up.
Setting: Tertiary rhinology centers.
Methods: Electronic patient record data from 116 CRSwNP patients (46 with NERD and 70 without NERD) undergoing ESS during 2001–17 were studied. Mean follow-up time was 9.9 years (range 1.1–15.3). Endpoints reflecting uncontrolled CRSwNP were revision ESS, and need for rescue/advanced therapy (e.g. antibiotics, oral corticosteroids and/or biological therapy) during follow-up. NERD was variable of interest and gender, age, asthma, allergic rhinitis (AR), smoking, Lund-Mackay (LM) score of sinus computed tomography scans previous ESS and baseline total ethmoidectomy were used as covariates.
Results: Twenty-one (49.7%) NERD patients and 18 (25.7%) non-NERD patients underwent revision ESS within a mean ± SD of 4.3 ± 2.8 and 3.7 ± 2.6 years, respectively (p = .013, by Logrank test). In Cox's regression models, NERD, female gender, young age, asthma, AR, previous ESS, and lack of total ethmoidectomy were associated with revision-ESS. In adjusted model, only the total ethmoidectomy predicted revision-free survival. In adjusted logistic regression model, there was an insignificant trend that NERD and LM score were associated with the need for rescue/advanced therapy in the follow-up.
Conclusions: Patients with NERD had higher risk of uncontrolled CRSwNP than patient group without NERD, as measured by revision ESS and/or need for rescue/advanced therapy in the follow-up. In addition, baseline total ethmoidectomy was associated with revision-free survival.

Keywords

chronic rhinosinusitis, computed tomography, diagnostics, endoscopic sinus surgery, paranasal sinuses, sinusitis

[1]Department of Otorhinolaryngology—Head and Neck Surgery, Helsinki University Hospital and University of Helsinki, Helsinki, Finland
[2]Skin and Allergy Hospital, Helsinki University Hospital and University of Helsinki, Helsinki, Finland
[3]Department of Otorhinolaryngology, Päijät-Häme Central Hospital, Lahti, Finland
[4]Department of Otorhinolaryngology, University of Tampere, Faculty of Medicine and Health Technology and Tampere University Hospital, Tampere, Finland

[5]Haartman Institute, University of Helsinki, Helsinki, Finland

Corresponding Author:
Sanna Katriina Toppila-Salmi, Haartmaninkatu 3, Haartman Institute, University of Helsinki, Helsinki 00014, Finland.
Email: sanna.salmi@helsinki.fi

Introduction

Chronic rhinosinusitis (CRS) is a heterogeneous group of inflammatory diseases of the nose and paranasal sinuses lasting for at least 12 weeks,[1] with a prevalence varying between 3–11%.[2,3] CRS has a severe impact on quality of life, which is comparable with asthma, chronic obstructive pulmonary disease, and diabetes.[2] The costs of CRS are substantial.[4,5] CRS phenotypes are CRS with nasal polyps (CRSwNP) and without (CRSsNP). Both have several molecular endotypes.[2] CRSwNP affects 0,5-4,5% of the general population.[1] Its pathogenesis is related to defects in the sinonasal epithelial cell barrier, increased exposure aberrant interactions between airway mucosa and microbiota/irritants.[1,6,7] CRSwNP patients tend to have more extensive sinus disease than patients with CRSsNP as measured by the 22 item Sino-Nasal Outcome Test (SNOT-22) score, sinus computed tomography (CT) Lund-Mackay (LM) –scores, and endoscopic Lund-Kennedy-scores.[1,8] Nonsteroidal anti-inflammatory drug exacerbated respiratory disease (NERD) has been reported in 8–26% of patients with CRSwNP.[9] NERD is characterized by severe eosinophilic hyperplastic inflammation of all sinuses and nasal passages as well as of the lower airways.[10,11]

A sudden worsening of preexisting symptoms suggests an exacerbation of CRS. European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2012 proposed the first definition of control in rhinosinusitis, which was slightly elaborated upon in the 2020 version.[1] It is based on a combined evaluation of symptom severity, nasal endoscopy and need for systemic medication (rescue treatment), and as such, CRS patients are defined as controlled, partly controlled or uncontrolled.

Several factors might associate with worsening of CRSwNP. CRSwNP patients have higher revision endoscopic sinus surgery (ESS) risk than CRSsNP patients.[12,13] High serum and tissue eosinophilia values of CRSwNP have been shown to be associated with higher recurrence rates.[14–17] In operated CRSwNP patients, higher preoperative endoscopic nasal polyp (NP) score, asthma, NERD, comorbid allergic sensitization, tissue interleukin-5 (IL-5) levels, and frontal sinus disease have higher risk for revision surgery.[18–23] Smoking has been shown to decrease the time before revision surgery in CRSwNP.[24] Postoperative SNOT-22 results can be used to predict the risk of revision surgery in CRS.[25]

There is some evidence that recurrence rate of ESS is lower after ESS with extended approaches compared with limited one.[1] A systemic Cochrane review showed that there is limited knowledge on whether isolated nasal polypectomy or more extensive sinus surgery is superior for CRSwNP.[26] A multicenter cohort study showed no difference in terms of health-related quality of life improvement between polypectomy and ESS.[27] However, some studies suggest that more extensive surgery (such as total ethmoidectomy) might be more effective than simple polypectomy or minimal invasive ESS.[28–31]

The aim was to compare postoperative control of CRSwNP in patients with/without NERD. Disease control was measured by using revision ESS rate and, need for rescue/advanced therapy (e.g. antibiotics, oral corticosteroids (OCS) and/or biological therapy) during follow-up. We hypothesized that patients with NERD have higher risk of uncontrolled CRSwNP than patients without NERD.

Methods

Setting

A retrospective hospital-based sample of CRSwNP patients in Finland with follow-up.

Subjects

This retrospective follow-up study was carried out at the Skin and Allergy Hospital of Helsinki University Hospital, and Departments of Otorhinolaryngology – Head and Neck Surgery, at Helsinki and Tampere University Hospitals between 2001 and 2020. The study design (nro 31/13/03/00/2015) was approved by the Research Ethics Committee of the above mentioned hospital districts and a study permission was granted.

We used electronic health record data of in total 116 CRSwNP patients who underwent consultation for ESS between 2003 and 2017 in the above-mentioned hospitals. The inclusion criterion was ESS in ≤1 year after the sinus CT scans taken for the baseline consultation visit (or the baseline visit, if CT data were not available) and this procedure was defined as the "baseline ESS". Previous sinonasal surgery was allowed.

The group of CRSwNP with NERD involved a random sample of 46 patients undergoing baseline ESS between 2003–16. NERD data was obtained from patient records: a history of wheeze/cough/naso-ocular symptoms after ingestion of NSAID were considered a sign of NERD. NERD diagnosis was additionally based on a positive reaction (wheeze and/or naso-ocular reaction) after intake of acetylsalicylic acid (ASA) at the hospital in two patients.

The group pf CRSwNP without NERD involved 70 patients undergoing baseline ESS between 2003–2017.

They were (i) twenty-six CRSwNP patients eligible (e.g. meeting with inclusion/exclusion criteria), from a random sample of 69 CRSwNP patients who had undergone nasal polyp biopsy during ESS consultation/ESS at Tampere University Hospital between 2005–2007; (ii) thirty-eight CRSwNP patients eligible from a random sample of 246 CRS patients who had undergone ESS consultation between 2002–2017 at the Helsinki and Tampere University Hospitals; (iii) six CRSwNP patients eligible form a random sample of 97 CRS/rhinitis patients who underwent sinus CT scans due to suspicion of CRS at Tampere University Hospital during 2006–2011.[32]

The exclusion criteria for both groups were age < 18 years, sinus CT signs of previous total ethmoidectomy in baseline CT scans, no patient record information of endoscopic NPs during baseline visit or baseline ESS, missing data of baseline operation or follow-up, ASA 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 EPOS 2012.[33] Baseline and follow-up ESS were performed by eight surgeons. After surgery, patients were instructed to use topical corticosteroids (either sprays or drops) regularly to prevent polyp regrowth, but topical corticosteroid rinses were not used.

Outcomes and Covariates

The follow-up data were collected from patient records on average (min-max) 9.9 (1.1–15.3) years after the baseline visit, until the last follow-up visit and/or corresponding patient record data of CRSwNP control. Two outcome measurements reflecting uncontrolled CRSwNP, were formed from the data: survival time until revision ESS or the end of follow-up; and need for rescue/advanced therapy, e.g. at least one of the following: (1.) >2 purchased doctor-prescribed antibiotic courses/year (2.) ≥1 purchased doctor-prescribed OCS courses/year and/or continuous OCS (3.) initiation of biological therapy during the follow-up. Electronic prescription and/or patient record data (if available) of the visit at the time of prescription were used to confirm that courses were prescribed 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 2018–2020, at least three years apart from the baseline ESS.

The data of covariates were collected from the hospital's patient records and sinus CT scans: gender, age, current smoking, allergic rhinitis (AR), asthma, previous ESS, and the extent of baseline ethmoidectomy. The definition of total ethmoidectomy was physician-reported opening of all ethmoidal cells ± additional operations (Table 1). Partial ethmoidectomy was defined as all other types of opening of ethmoidal cells ± additional operations. Polypectomy was defined as removal of NPs without opening of bony walls of ethmoidal cells ± middle meatal antrostomy. Asthma diagnosis was based on patient record documentation on typical history and asthma symptoms, and findings of lung function test (spirometry and peak expiratory flow (PEF)) of at least 15% improvement with bronchodilator test in spirometry (in forced expiratory flow volume in one second (FEV1) or in forced vital capacity (FVC)) and/or recurrent 20% diurnal variation in PEF monitoring or recurrent 15% bronchodilator response in PEF monitoring or positive methacholine challenge test (moderate to severe bronchial hyperresponsiveness). NERD diagnosis was based on a positive patient history of wheeze/cough or naso-ocular symptoms after intake of NSAID.[34] A doctor-diagnosed AR was based on positive skin prick test or serum specific IgE results, in addition to typical symptoms.

Statistics

For the statistical analysis SPSS Base 24 Statistical Software Package (SPSS Inc., Chicago, IL, USA) was used. The associations between predictor/covariates and outcomes of uncontrolled CRSwNP during follow-up were estimated using Fisher's exact test (dichotomous), and Kruskal-Wallis and Mann Whitney U test (continuous). Kaplan-Meier method and logrank test were used in revision-free survival models. Cox's proportional hazards model was used to evaluate the hazard ratio (HR) of revision ESS rate between different background variables. Each predisposing factor was modelled separately. The background variables that were associated significantly with revision ESS, were entered into the multivariable model. P-values < 0.05 were considered statistically significant.

Results

Of the total of 116 CRSwNP patients, 53 (46%) were females, 50 (43%) had history of AR, 66 (57%) had asthma, 46 (40%) had NERD, and 23 (20%) were current smokers. At the baseline, the mean age ± SD was 48.6 ± 15.4 years. All patients underwent ESS within one year after the baseline consultation visit. Sixty patients (52%) did not have a history of previous ESS (Table 1). Patients with NERD were more often females and they had more often asthma diagnosis, higher median number of previous ESS, and higher median LM-score than patients without NERD (Table 1).

Table 1. Comparison Between Two Subject Groups: CRSwNP With NERD and CRSwNP Without NERD.

	CRSwNP Without NERD N = 70	CRSwNP With NERD N = 46	P
Gender, n (%)			
Female	23 (32.9)	30 (65.2)	**.001**
Male	47 (67.1)	16 (34.8)	
Age, median (Q1–Q3)	48.8 (39.5–59.0)	50.0 (37.8–58.9)	.82
Smoking, n (%)			
No	53 (77.9)	37 (82.2)	.64
Current	15 (22.1)	8 (17.8)	
Asthma			
No	46 (65.7)	3 (6.7)	**<.001**
Yes	24 (34.3)	42 (93.3)	
Allergic rhinitis			
No	45 (64.3)	20 (44.4)	.053
Yes	25 (35.7)	25 (55.6)	
≥4 antibiotic courses /year			
No	44 (74.6)	26 (70.3)	.65
Yes	15 (25.4)	11 (29.7)	
≥1 peroral corticosteroid course /year			
No	41 (58.6)	23 (50.0)	.45
Yes	29 (41.4)	23 (50.0)	
NP eosinophilia			
< 30%	28 (49.1)	12 (37.5)	.38
≥30%	29 (50.9)	20 (62.5)	
Baseline NP score, median (Q1–Q3)	4 (3–6)	5 (4–6)	.076
Total number of previous CRS surgeries, median (Q1–Q3)	0 (0–1.25)	1 (0–2)	**.046**
A history of previous ESS			
No	42 (58.6)	18 (40.0)	.18
Polypectomy (PP) ±middle/inferior meatal antrostomy (MMA/IMA)	19 (27.1)	15 (33.3)	
PP + partial ethmoidectomy ± MMA ± frontal recess surgery (FRS)	7 (10.0)	9 (20.0)	
PP + total ethmoidectomy ± MMA	1 (1.4)	0 (0)	
MMA/IMA without PP	1 (1.4)	3 (6.7)	
Baseline sinus CT scans			
CT scans were available	58 (82.9)	40 (87.0)	.61
Total Lund-Mackay score, median (Q1–Q3)	14 (12–17.5)	15 (14–21.5)	**.010**
Sum of the ethmoid Lund-Mackay scores, median (Q1–Q3)	4 (4–6)	6 (4–8)	**.025**
Previous ESS signs of the baseline sinus CT scans	30 (51.7)	30 (75.0)	**.022**
Total removal of uncinated process	7 (12.1)	11 (27.5)	.066
Opening of the infundibulum	8 (13.8)	10 (25.0)	.19
Opening of the bulla ethmoidalis	6 (10.3)	4 (10.0)	1.0
Opening of the basal lamella	1 (1.7)	1 (2.5)	1.0
Full anterior ethmoidectomy (up to frontal recess)	1 (1.7)	1 (2.5)	1.0
Full posterior ethmoidectomy	0 (0)	0 (0)	–
Entrance of the frontal recess without performing adequate Draf 2a	2 (3.4)	0 (0)	.51
Draf 2a	2 (3.4)	0 (0)	.51
Opening of the sphenoid	0 (0)	0 (0)	-
Baseline ethmoidectomy			
No	22 (31.4)	20 (43.5)	.39
Partial	32 (45.7)	19 (41.3)	
Total	16 (22.9)	7 (15.2)	
Baseline surgery performed in addition to ethmoidectomy			
Polypectomy (PP)[3]	17 (24.6)	14 (31.1)	.64
PP + middle meatal antrostomy[4] (MMA) ±inferior meatal antrost. (IMA)	49 (71.0)	27 (60.0)	
PP + frontal recess surgery/balloon (FRS) ±MMA	2 (2.9)	2 (4.4)	
PP+ sfenoidectomy ±MMA±FRS	1 (1.4)	2 (4.4)	

Table I. Continued.

	CRSwNP Without NERD N = 70	CRSwNP With NERD N = 46	P
Revision ESS performed during the follow-up			
No	52 (74.3)	25 (54.3)	**.016**
Polypectomy (PP) ±middle/inferior meatal antrostomy (MMA/IMA)	6 (8.6)	6 (13.0)	
PP + partial ethmoidectomy ± MMA ± frontal recess surgery (FRS)	10 (14.3)	6 (13.0)	
PP + total ethmoidectomy ± MMA	2 (2.9)	9 (19.6)	

NERD = nonsteroidal anti-inflammatory drug exacerbated respiratory disease; CRS = chronic rhinosinusitis; AR = allergic rhinitis; NP = nasal polyps; FRS = frontal recess surgery; MMA = middle meatal antrostomy; RFA = radiofrequency ablation. P values by Fisher's exact test (dichotomous variables) or Mann Whitney U test (continuous variables). Q1 = 25% percentile, Q3 = 75% percentile. Polypectomy = removal of polyps ± middle meatal maxillary antrostomy without ethmoidectomy Partial ethmoidectomy = anterior/partial ethmoidectomy in addition to polypectomy. Total ethmoidectomy = total ethmoidoctomy in addition to polypectomy; [3]One patient had additional septoplasty and middle turbinate resection. [4]Six patients had additional operations: inferior turbinate RFA (n = 4), septoplasty (n = 1), dental extractions (n = 1).
All subjects underwent endoscopic sinus surgery (ESS) at baseline.
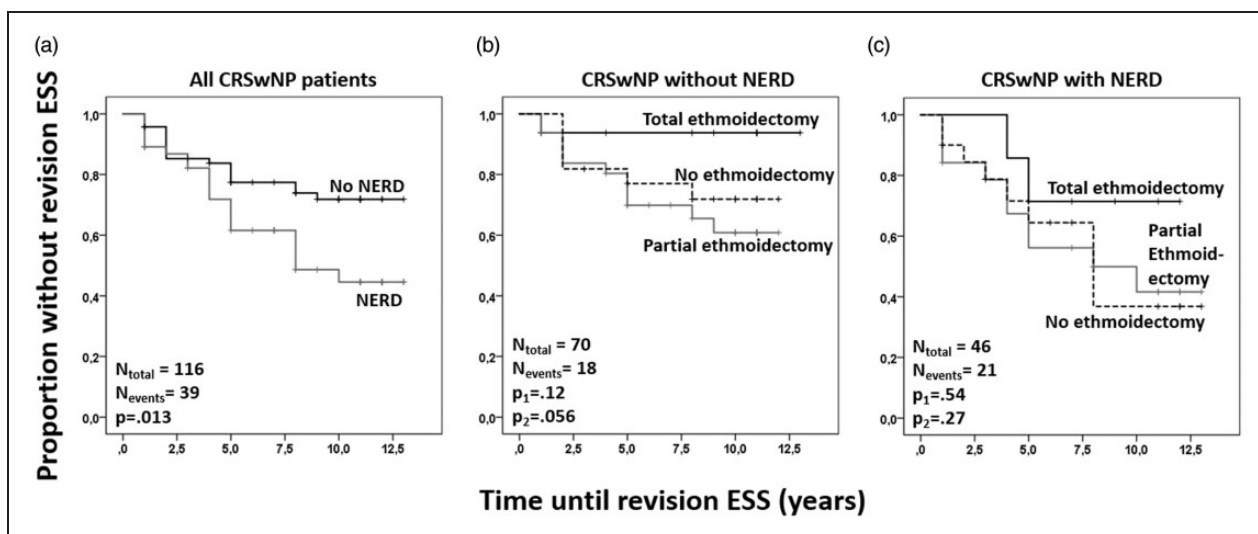Statistically significant p values (<.05) are in bold.

Figure 1. Revision-free survival models according to the Kaplan-Meier method. Predictive effect of (a) NERD and (b and c) extent of baseline ethmoidectomy to the time until revision endoscopic sinus surgery (ESS). P-values by log rank test. p_1 = general; p_2 = total ethmoidectomy vs. polypectomy or partial ethmoidectomy.

Revision-Free Survival

Twenty-one (49.7%) NERD patients and 18 (25.7%) non-NERD patients underwent revision ESS within a mean ± SD of 4.3 ± 2.8 and 3.7 ± 2.6 years, respectively. The over all follow-up time was 9.6 ± 3.8 years in NERD group and 10.0 ± 3.2 years in non-NERD group. In the survival analyses the mean (min-max) follow-up time was 7.1 ± 3.8 years until the first revision surgery/2019, whichever came first. We formed a revision-free survival curve with logrank test, in which the predictor variables were NERD (Figure 1(A)) or, baseline polypectomy/partial/total ethmoidectomy in subgroups without/with NERD (Figure 1(B) and (C)). NERD was associated with increased revision ESS risk when comparing with the patients without NERD (Figure 1(A)). When observing the non-NERD group, baseline partial ethmoidectomy or baseline polypectomy was associated with increased revision ESS risk as compared with baseline total ethmoidectomy (Figure 1(B)). Yet in the NERD group, baseline total ethmoidectomy was not statistically significantly associated with revision-free survival (Figure 1(C)).

Cox's proportional hazards model was used to investigate the association between the revision-free survival time until the revision ESS, and the predictors. In a univariate model, NERD, female gender, young age, asthma, AR, previous ESS, and lack of total ethmoidectomy were associated with revision-ESS in the follow-up (Table 2). In a multivariable model, only total ethmoidectomy at baseline was associated with revision-free survival (Table 2).

Table 2. Unadjusted and Adjusted Cox's Proportional Hazard Model for the Variables Analyzed Fitted for the Need for Revision Endoscopic Sinus Surgery (ESS) During the Follow-up of on Average 9.9 Years.

	N All	N (%) Events	HR (95% CI)	P-Value	Adjusted HR (95% CI)	P-Value
NERD						
No	70	18 (25.7)	1		1	
Yes	46	21 (45.7)	2.13 (1.13–4.00)	.019	1.15 (0.50–2.63)	.75
Gender						
Male	63	15 (23.8)	1		1	
Female	53	24 (45.3)	2.25 (1.18–4.29)	.014	1.52 (0.73–3.17)	.26
Age			0.97 (0.95–1.00)	.021	0.98 (0.95–1.00)	.073
Current smoking						
No	90	31 (34.4)	1			
Yes	23	8 (34.8)	0.88 (0.40–1.91)	.75	Not entered	
Asthma						
No	49	11 (22.4)	1		1	
Yes	66	28 (42.4)	2.45 (1.22–4.95)	.012	1.89 (0.71–5.06)	.21
AR						
No	65	18 (27.7)	1		1	
Yes	50	21 (42.0)	1.91 (1.02–3.60)	.045	0.85 (0.38–1.87)	.68
LM score			1.06 (0.99–1.15)	.12	Not entered	
Previous ESS						
No	60	15 (25.0)	1		1	
Yes	56	24 (42.9)	2.13 (1.12–4.08)	.022	1.69 (0.86–3.33)	.13
Baseline ethmoidectomy						
Total	23	3 (13.0)	1		1	
Partial	51	21 (41.2)	3.75 (1.12–12.56)	.033	3.52 (1.03–11.98)	.044
No (poly-pectomy)	42	15 (35.7)	3.30 (0.95–11.39)	.060	3.48 (0.99–12.23)	.052

NERD = nonsteroidal anti-inflammatory drug exacerbated respiratory disease; AR= allergic rhinitis HR=Hazard ratio, CI=confidence interval. Only the variables that had significant p values (<.05, marked with bold font) in univariate model were entered into the multivariable model. Polypectomy = removal of polyps ± middle meatal maxillary antrostomy without ethmoidectomy; Partial ethmoidectomy = anterior/partial ethmoidectomy in addition to poly-pectomy; Total ethmoidectomy = total ethmoidectomy in addition to polypectomy.

Rescue/Advanced Therapy in the Follow-up

Medication data for the follow-up period 2018–2020 were available for 112/116 (96,6%) patients. This patient group data was analyzed in univariate and multivariable logistic regression models to find background variables associating with the need for rescue/advanced therapy in the follow-up. In the univariate model, NERD, asthma, and high LM score at baseline were associated with the need for rescue/advanced therapy in the follow-up (Table 3). When entering these three variables into the multivariable model, there was an insignificant trend that NERD and LM score were associated with the need for rescue/advanced therapy in the follow-up (Table 3).

Discussion

The purpose of this retrospective follow-up study was to compare postoperative control of CRSwNP patients between NERD and non-NERD groups. We found that NERD group had higher risk of uncontrolled CRSwNP than non-NERD group. We used two outcome measurement variables for uncontrolled CRSwNP: revision ESS-rate and need for rescue/advanced therapy in the follow-up. This is in line with previous observations that have shown by using different outcome variables that CRSwNP patients with asthma or NERD have a increased risk for uncontrolled disease compared with CRSwNP without these comorbidities.[18,21–23,31,35] CRSwNP patients with comorbid asthma and/or NERD patients have shown to benefit from ESS, yet long-term recurrence seems more common with these comorbidities.[23,36,37]

We also found in adjusted models that baseline total ethmoidectomy was associated with revision-free survival. This finding was more pronounced in the group without NERD than in the NERD group. This may reflect a more severe disease and a greater tendency for polyps to grow in NERD, despite the extent of baseline surgery. The literature has shown that CRSwNP patients with NERD have higher levels of serum and tissue eosinophils than CRSwNP without NERD, and both serum and tissue eosinophilia has been shown to predict polyps regrowth and ESS revisions.[11,14–17] There is

Table 3. Univariate and Multivariable Binary Logistic Regression Models for the Background Variables Analyzed Fitted for the Need for Rescue/Advanced Therapy in the Follow-up.

	N All	N (%) Events	OR (95% CI)		Adjusted OR (95% CI)	
NERD						
No	68	12 (17.6)	1		1	
Yes	44	19 (43.2)	3.55 (1.50–8.41)	**.004**	2.85 (0.89–9.16)	.079
Gender						
Male	61	14 (23.0)	1			
Female	51	17 (33.3)	1.68 (0.73–3.86)	.22	Not entered	
Age						
			0.99 (0.96–1.02)	.35	Not entered	
Current smoking						
No	87	26 (29.9)	1			
Yes	22	4 (18.2)	0.52 (0.16–1.69)	0.28	Not entered	
Asthma						
No	47	8 (17.0)	1		1	
Yes	64	22 (34.4)	2.55 (1.02–6.40)	**.046**	1.29 (0.37–4.55)	.69
AR						
No	62	16 (25.8)	1			
Yes	49	14 (28.6)	1.15 (0.50–2.67)	.75	Not entered	
LM score			1.14 (1.03–1.27)	**.012**	1.11 (1.00–1.24)	.055
Previous ESS						
No	58	13 (22.4)	1			
Yes	54	18 (33.3)	1.73 (0.75–4.00)	.20	Not entered	
Baseline ethmoidectomy						
Total	23	6 (26.1)	1			
Partial	49	15 (30.6)	1.25 (0.41–3.80)	.69	Not entered	
No (poly-pectomy)	40	10 (25.0)	0.94 (0.29–3.06)	.92		

The rescue/advanced therapy was defined as at least one of the following: (1.) >2 purchased doctor-prescribed antibiotic courses/year (2.) ≥1 purchased doctor-prescribed OCS/year and/or continuous OCS (3.) initiation of biological therapy during the follow-up . The data was not available from 4 patients. Bold values denote statistical significance at the p < 0.05 level. The second model is a multivariable model adjusted by the background variables that were associated at p < 0.05 level in the first model. NERD= non-steroidal anti-inflammatory drug exacerbated respiratory disease.

limited knowledge of effect of extent of ethmoidal surgery on the revision ESS rate. Jankowski et al. has shown that more extensive surgery (nasalization of the ethmoids) was associated with lesser polyp recurrence.[29] Browne et al. has concluded that nasal polypectomy with additional surgery seems to have no benefit over simple polypectomy in terms of health-related quality of life improvement.[27] The study by Wu et al. has shown that the median time to revision surgery was longer in patients who underwent middle turbinate resection rather than preservation.[24] Mastersson et al. has reported that extensive ESS had lower revision surgery rate compared to polyposis surgery limited to anterior ethmoids.[30] Bassioni and Wormald has shown that Draf 3 frontal sinusotomy reduced the prevalence of polyp recurrence.[21] Thus, most previous studies seem to be in line with the results presented in our study, which indicate that extended surgery might lead to better disease control in CRSwNP than limited surgery. However, a Cochrane review in 2014 has not identified any trials which would have met their inclusion criteria.[26]

Studies suggest that more extensive sinus surgery could be more effective than limited surgery in the treatment of CRSwNP.[21,24,29,30] However, as mentioned in the EPOS 2020, the weight of evidence for extended approaches lies in revision cases, not in primary surgeries.[1] When choosing between limited or extended surgery, the potential disadvantages and financial implications as well as the available hospital resources should be considered. A Japanese group showed in a database analysis of 50,734 patients, that the extent of ESS did not significantly affect the overall complication rate, but multiple sinus surgery was associated with a higher rate of orbital injury comparing with single sinus surgery or with surgery for all the sinuses.[38] However, extended surgery is more expensive and requires more operating room time.[38,39] In future studies, it should be assessed whether the higher costs of extended surgery will lead to a reduction in subsequent healthcare costs.

In our study about a half of the patients had undergone one or more previous ESS, which was a

predictor of the need for revision ESS in the follow-up in unadjusted model. Yet previous ESS was not associated with recurrence-free survival in adjusted model. It has been reported earlier that revision rate is higher in CRSwNP if the patient has a history of previous surgery,[19,23] but the finding has not been consistent in all reports.[24,40]

We acknowledge that in order to reduce variables in statistical models, we focused on observing the extent of ethmoidectomy although also surgery of other paranasal sinuses could have had affected the results. Middle meatal antrostomy was performed in the most of baseline surgery cases yet, patient record data was not available of the extent of middle meatal antrostomy. Frontal surgery was performed in only a few baseline cases. Thus a prospective study with increased subject number would be warranted. Other limitations of this retrospective study include small sample size and lack of a standardized patient-reported outcome measurement. We acknowledge that due to retrospective nature of this study, proper data was not available if the patients had used intranasal corticosteroids postoperatively according to instructions, which could have affected the results. Our analysis of revision surgery may have been influenced by several factors unrelated to the recurrence of CRS, including waiting times for surgery, patients' preferences to delay surgery for personal reasons, the patient's tolerance of recurrent sinusitis symptoms, baseline operative technique, and the surgeon's opinion as to when revision surgery is clinically warranted. It is also possible that a patient may have changed to private hospital leading to a slight possibility that no accurate follow-up data was available On the other hand, public medical care covers over 90% of operations in Finland[41] and the patients who were no longer in hospital follow-up were followed up by reviewing electronic prescriptions, which would minimize this source of possible bias.

Conclusion

This retrospective cohort of CRSwNP patients showed that NERD group had higher risk of uncontrolled disease than patient group without NERD as measured by revision ESS and/or need for rescue/advanced therapy in the follow-up. In addition, baseline total ethmoidectomy was associated with revision-free survival.

Ethical Approval

This study was approved by our institutional review board.

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

There are no human subjects in this article and informed consent is not applicable.

Authors' Contributions

Markus Jukka Lilja: Author has participated in study planning, data collection, data management, and manuscript preparation.
Anni Koskinen: Author has participated in study planning, data collection, data management, and manuscript preparation.
Paula Virkkula: Author has participated in study planning, data collection, data management, and manuscript preparation.
Seija Inkeri Vento: Author has participated in study planning, data collection, data management, and manuscript preparation.
Jyri Myller: Author has participated in study planning, data collection, data management, and manuscript preparation.
Sari Hammarén-Malmi: Author has participated in study planning, data collection, data management, and manuscript preparation.
Anu Laulajainen-Hongisto: Author has participated in study planning, data collection, data management, and manuscript preparation.
Maija Hytönen: Author has participated in study planning, data collection, data management, and manuscript preparation.
Antti Mäkitie: Author has participated in study planning, data collection, data management, and manuscript preparation.
Jura Numminen: Author has participated in study planning, data collection, data management, and manuscript preparation.
Saara Sillanpää Author has participated in study planning, data collection, data management, and manuscript preparation.
Hannu Raitiola: Author has participated in study planning, data collection, data management, and manuscript preparation.
Markus Rautiainen: Author has participated in study planning, data collection, data management, and manuscript preparation.
Sanna Katriina Toppila-Salmi: Author has planned and directed the study and participated in data collection, data management, and manuscript preparation.

ORCID iDs

Markus Jukka Lilja ⦿ https://orcid.org/0000-0003-1781-1718
Paula Virkkula ⦿ https://orcid.org/0000-0003-4224-5201
Anu Laulajainen-Hongisto ⦿ https://orcid.org/0000-0001-5109-6944
Sanna Katriina Toppila-Salmi ⦿ https://orcid.org/0000-0003-0890-6686

References

1. Fokkens WJ, Lund VJ, Hopkins C, et al. European position paper on rhinosinusitis and nasal polyps 2020. *Rhinology*. 2020;58(1):1–464.

2. Hastan D, Fokkens WJ, Bachert C, et al. Chronic rhinosinusitis in europe–an underestimated disease. A GA(2) LEN study. *Allergy*. 2011;66(9):1216–1223.

3. 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):1207–1214.

4. Smith KA, Orlandi RR, Rudmik L. Cost of adult chronic rhinosinusitis: a systematic review. *Laryngoscope*. 2015;125(7):1547–1556.

5. Lourijsen ES, Fokkens WJ, Reitsma S. Direct and indirect costs of adult patients with chronic rhinosinusitis with nasal polyps. *Rhinology*. 2020;58(3):213–217.

6. Toppila-Salmi S, van Drunen CM, Fokkens WJ, et al. Molecular mechanisms of nasal epithelium in rhinitis and rhinosinusitis. *Curr Allergy Asthma Rep*. 2015;15(2):495.

7. Hulse KE. Immune mechanisms of chronic rhinosinusitis. *Curr Allergy Asthma Rep*. 2016;16(1):1.

8. Dennis SK, Lam K, Luong A. A review of classification schemes for chronic rhinosinusitis with nasal polyposis endotypes. *Laryngoscope Investig Otolaryngol*. 2016;1(5):130–134.

9. Kowalski ML, Agache I, Bavbek S, et al. Diagnosis and management of NSAID-exacerbated respiratory disease (N-ERD)-a EAACI position paper. *Allergy*. 2019;74(1):28–39.

10. Stevens WW, Schleimer RP. Aspirin-exacerbated respiratory disease as an endotype of chronic rhinosinusitis. *Immunol Allergy Clin North Am*. 2016;36(4):669–680.

11. Steinke JW, Payne SC, Borish L. Eosinophils and mast cells in aspirin-exacerbated respiratory disease. *Immunol Allergy Clin North Am*. 2016;36(4):719–734.

12. Smith KA, Orlandi RR, Oakley G, et al. Long-term revision rates for endoscopic sinus surgery. *Int Forum Allergy Rhinol*. 2019;9(4):402–408.

13. Koskinen A, Salo R, Huhtala H, et al. Factors affecting revision rate of chronic rhinosinusitis. *Laryngoscope Investig Otolaryngol*. 2016;1(4):96–105.

14. Brescia G, Barion U, Zanotti C, Giacomelli L, Martini A, Marioni G. The prognostic role of serum eosinophil and basophil levels in sinonasal polyposis. *Int Forum Allergy Rhinol*. 2017;7(3):261–267.

15. Lou H, Meng Y, Piao Y, et al. Predictive significance of tissue eosinophilia for nasal polyp recurrence in the Chinese population. *Am J Rhinol Allergy*. 2015;29(5):350–356.

16. Brescia G, Pedruzzi B, Barion U, et al. Are neutrophil-, eosinophil-, and basophil-to-lymphocyte ratios useful markers for pinpointing patients at higher risk of recurrent sinonasal polyps? *Am J Otolaryngol*. 2016;37(4):339–345.

17. Brescia G, Marioni G, Franchella S, et al. A prospective investigation of predictive parameters for post-surgical recurrences in sinonasal polyposis. *Eur Arch Otorhinolaryngol*. 2016;273(3):655–660.

18. Mendelsohn D, Jeremic G, Wright ED, et al. Revision rates after endoscopic sinus surgery: a recurrence analysis. *Ann Otol Rhinol Laryngol*. 2011;120(3):162–166.

19. DeConde AS, Mace JC, Levy JM, et al. Prevalence of polyp recurrence after endoscopic sinus surgery for chronic rhinosinusitis with nasal polyposis. *Laryngoscope*. 2017;127(3):550–555.

20. 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(1):1–11.

21. Bassiouni A, Wormald PJ. Role of frontal sinus surgery in nasal polyp recurrence. *Laryngoscope*. 2013;123(1):36–41.

22. 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.

23. Wynn R, Har-El G. Recurrence rates after endoscopic sinus surgery for massive sinus polyposis. *Laryngoscope*. 2004;114(5):811–813.

24. Wu AW, Ting JY, Platt MP, et al. Factors affecting time to revision sinus surgery for nasal polyps: a 25-year experience. *Laryngoscope*. 2014;124(1):29–33.

25. Rudmik L, Soler ZM, Hopkins C. Using postoperative SNOT-22 to help predict the probability of revision sinus surgery. *Rhinology*. 2016;54(2):111–116.

26. Sharma R, Lakhani R, Rimmer J, et al. Surgical interventions for chronic rhinosinusitis with nasal polyps. *Cochrane Database Syst Rev*. 2014;11:CD006990.

27. Browne JP, Hopkins C, Slack R, et al. Health-related quality of life after polypectomy with and without additional surgery. *Laryngoscope*. 2006;116(2):297–302.

28. Chen FH, Deng J, Hong HY, et al. Extensive versus functional endoscopic sinus surgery for chronic rhinosinusitis with nasal polyps and asthma: a 1-year study. *Am J Rhinol Allergy*. 2016;30(2):143–148.

29. Jankowski R, Pigret D, Decroocq F, et al. Comparison of radical (nasalisation) and functional ethmoidectomy in patients with severe sinonasal polyposis. A retrospective

study. *Rev Laryngol Otol Rhinol (Bord)*. 2006;127(3):131–140.

30. Masterson L, Tanweer F, Bueser T, et al. Extensive endoscopic sinus surgery: Does this reduce the revision rate for nasal polyposis? *Eur Arch Otorhinolaryngol*. 2010;267(10):1557–1561.

31. Zhang L, Zhang Y, Gao Y, et al. Long-term outcomes of different endoscopic sinus surgery in recurrent chronic rhinosinusitis with nasal polyps and asthma. *Rhinology*. 2020;58(2):126–135.

32. Julkunen A, Terna E, Numminen J, et al. Inter-observer agreement of paranasal sinus computed tomography scans. *Acta Otolaryngol*. 2017;137(6):611–617.

33. 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.

34. Global Initiative for Asthma. Global strategy for asthma management and prevention. www.ginasthma.org. Published 2018. Accessed March 8, 2021.

35. 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):282–290.

36. Laulajainen-Hongisto A, Turpeinen H, Vento SI, et al. High discontinuation rates of peroral ASA treatment for CRSwNP: A real-world multicenter study of 171 N-ERD patients. *J Allergy Clin Immunol Pract*. 2020.

37. Jantti-Alanko S, Holopainen E, Malmberg H. Recurrence of nasal polyps after surgical treatment. *Rhinol Suppl*. 1989;8:59–64.

38. Suzuki S, Yasunaga H, Matsui H, et al. Complication rates after functional endoscopic sinus surgery: analysis of 50,734 Japanese patients. *Laryngoscope*. 2015;125(8):1785–1791.

39. Thomas AJ, Smith KA, Newberry CI, et al. Operative time and cost variability for functional endoscopic sinus surgery. *Int Forum Allergy Rhinol*. 2019;9(1):23–29.

40. Lee JY, Lee SW, Lee JD. Comparison of the surgical outcome between primary and revision endoscopic sinus surgery for chronic rhinosinusitis with nasal polyposis. *Am J Otolaryngol*. 2008;29(6):379–384.

41. Toppila-Salmi S, Rihkanen H, Arffman M, et al. Regional differences in endoscopic sinus surgery in Finland: a nationwide register-based study. *BMJ Open*. 2018;8(10): e022173.