Treatment escalation and sustained disease control in chronic rhinosinusitis: a retrospective surgical cohort study

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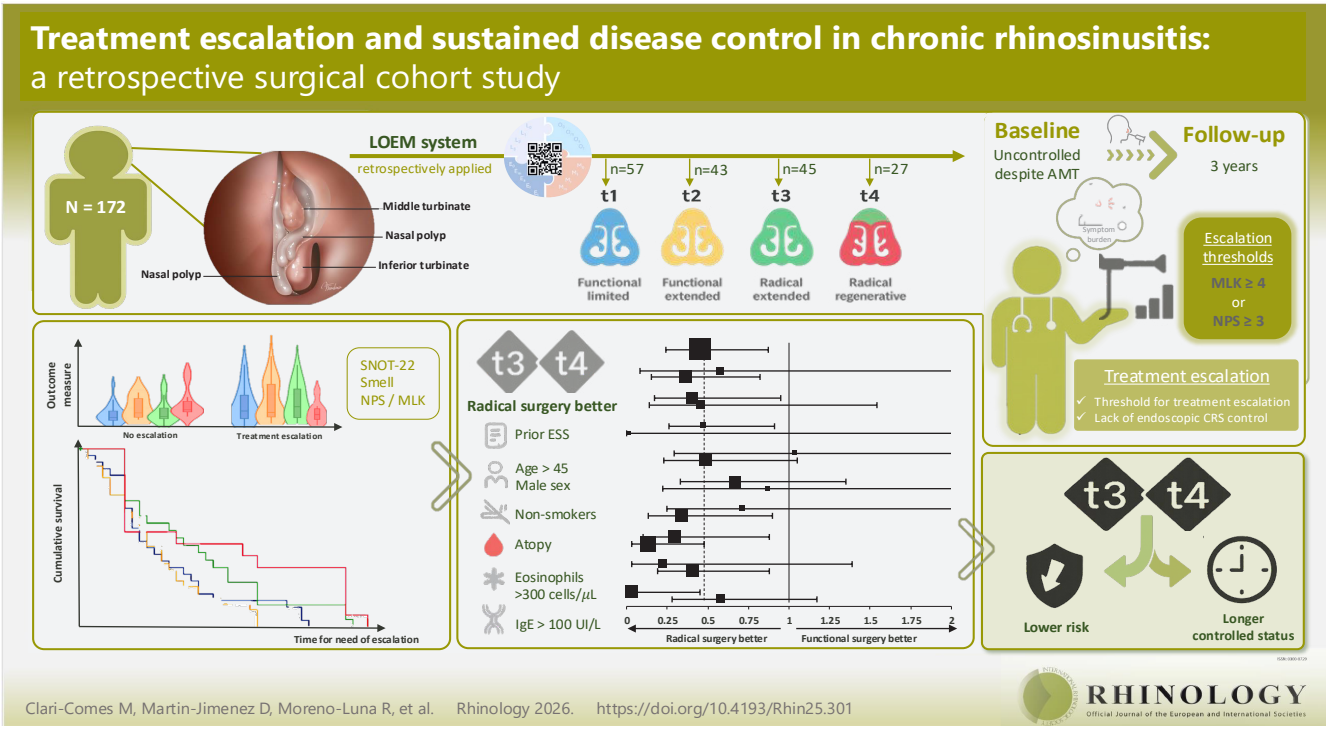

Abstract

Background: The impact of endoscopic sinus surgery (ESS) extent on long-term disease control and therapeutic escalation in chronic rhinosinusitis with nasal polyps (CRSwNP) remains unclear. This study aims to evaluate the clinical applicability of endoscopy-based criteria for therapeutic escalation and to determine the impact of surgical extent on the risk and timing of treatment intensification. **Methods**: A retrospective cohort study with 3-year follow-up was conducted. CRSwNP patients who underwent ESS were included and classified according to Lamella Ostium Extent Mucosa (LOEM) system (t1–t4). Baseline characteristics and disease severity measures were assessed. Therapeutic escalation was defined by endoscopic criteria. Predictors of escalation and the effect of ESS extent on escalation timing across clinical phenotypes were analyzed using multivariate logistic regression, Kaplan-Meier curves and Cox regressions. **Results**: In the overall sample (n=172), patients who required escalation showed higher SNOT-22 scores and poorer olfactory function. More extensive ESS (LOEM t3–t4) was associated with significantly reduced escalation risk and prolonged disease control. Post hoc analyses confirmed significant pairwise differences favoring extensive (t3–t4) over limited (t1–t2) surgery. Subgroup analyses demonstrated greater benefits in older subjects, atopic patients, revision surgeries and patients with eosinophils >300cells/µL. Higher baseline SNOT-22 scores remained an independent predictor of escalation after ESS. **Conclusions**: Surgical extent appears to influence both escalation risk and timing. More extensive ESS may provide more sustained control, particularly in revision cases and biomarker-defined subgroups, supporting its integration into personalized algorithms.

Key words: nasal surgical procedures, paranasal sinuses, rhinosinusitis, sinusitis, type-2 inflammation

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Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a persistent inflammatory disease of the sinonasal mucosa that significantly impairs patients' quality-of-life (QoL) and imposes a substantial economic burden on healthcare systems [1,2]. Initial treatment typically involves topical and oral treatments, with endoscopic sinus surgery (ESS) reserved for cases unresponsive to appropriate medical therapy [3]. However, even following surgery, achieving clinical remission remains a substantial challenge, even with the adjuvant use of biologic therapies, with many patients requiring multiple surgical interventions over time [4–6].

Within this evolving framework, the management strategies have shifted toward reducing the clinical burden to levels acceptable for patients, a concept that has come to be defined as disease control [7,8]. In this regard, assessment of clinical status often presents limitations, given the widespread tendency to primarily employ patient-reported outcome measures. While these tools have recognized clinical value, their subjective nature limits the accurate quantification of disease impact and hampers the establishment of standardized criteria for defining disease control [9,10]. To address this limitation, the concept of treatment escalation has recently been proposed, based on findings from nasal endoscopy [11]. This approach relies on measurable parameters, such as polyp size, mucosal edema or nasal secretions, to define the degree of disease control and, alternatively, identify the need for therapy modification.

In addition to the challenges in achieving CRSwNP control, the high failure rate observed in this condition is multifactorial [12], largely attributable to poorly defined phenotypes and the lack of consensus regarding the scope of ESS, both of which have hindered the development of precision surgical approaches [13,14]. The recent introduction of new classification systems has helped generate higher-quality scientific evidence [15,16]. In this context, an association has been identified between the extent of surgery and improvements in both QoL and endoscopic findings, as well as a particularly favorable response of certain phenotypes to more extensive mucosal surgical procedures [17]. Therefore, the aim of the present study is to evaluate the clinical applicability of the therapeutic escalation concept based on endoscopic findings in the surgical management of CRSwNP patients and to determine whether the extent of surgery influences the timing of treatment intensification during follow-up.

Materials and methods

Study design

A retrospective cohort study analyzed CRSwNP patients who met full eligibility criteria and completed the predefined follow-up protocol. The sample was divided into four surgical groups, according to Lamella Ostium Extent Mucosa (LOEM) classification [15].

Setting

The study was conducted at the rhinology unit of a tertiary hospital between 2019 and 2024, including data systematically collected from patients' medical records, before and up to three years after surgery. The study protocol was reviewed and approved by the Institutional Ethics Committee (approval No. 2706-N-20).

Participants

Inclusion criteria were adults with a CRSwNP diagnosis based on the EPOS 2020 and POLINA 2023 criteria [18,19], who had not responded to appropriate medical treatment and reported a moderate-to-severe impact on the Sinonasal Outcome Test (SNOT)-22 [20]. Excluded from the study were: pregnant/breast-feeding women, patients with eosinophilic granulomatosis with polyangiitis or severe systemic diseases (except asthma or NSAIDs exacerbated respiratory disease –N-ERD–), neoplasms or pathologies related to the abuse of vasoconstrictor agents, and patients with absence of polyps and unilateral nasal inflammatory diseases. Patients treated with monoclonal antibodies during the study period were also excluded, to minimise potential confounding of surgery-related outcomes by the effects of biologic therapy.

Variables

Demographic, clinical (asthma, N-ERD, prior ESS, smoking, atopy, therapy with systemic steroid –SCS–) and laboratory data (serum eosinophilia, total immunoglobulin –Ig– E) were collected. Disease burden was evaluated in terms of QoL, endoscopic findings and radiologic imaging.

Four LOEM-defined surgical types (t1-t4) were considered [15]: t1 with functional limited intervention targeting the lamella and ostia, as well as limited mucosal removal to maintain mucociliary function and sinus aeration; t2 which entailed a functional extended approach ranging from interventions involving at least two lamellae and enlargement of at least two natural ostia to a complete opening of all paranasal sinus drainage pathways (full-house functional ESS), with mucosal resection limited to diseased areas; t3, consisting of radical extended surgery, including a complete sphenoethmoidectomy, partial maxillectomy and at least a bilateral Draf 2A frontal sinusotomy, with complete mucosal resection (i.e., reboot technique) [21]; and finally, t4 which involved complete mucosal removal, followed by a regenerative technique (mucoplasty) [22].

More extended approaches (t3-t4) were generally performed in patients with one or more poor prognostic factors (e.g., uncontrolled asthma, severe N-ERD or ≥2 prior ESS), as well as extensive sinus opacities (i.e., CT-scan Lund Mackay (LM) score ≥14 points). In contrast, functional ESS (t1-t2) was preferred for patients with absence or well-controlled comorbidities and/or

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partial sinus CT opacities. Asthma control was evaluated clinically, considering medical history, treatment requirements and the specialist judgment of pulmonologists or allergists involved in multidisciplinary care. A more detailed description of these surgical indications and representative endoscopic and radiological images is provided in Table S1.

In this study, the primary outcome was the need for therapeutic escalation, defined based on endoscopic assessments: modified Lund-Kennedy (MLK) score ≥4 or nasal polyps score (NPS) ≥3. These thresholds were established by a recent international expert consensus, that identified the cut-offs as the most consistent and reproducible criteria for indicating loss of endoscopic CRSwNP control and prompting consideration of treatment escalation. Conversely, MLK <4 or NPS <3 were regarded as achievable endoscopic treatment goals associated with stable disease [11]. This approach follows the EPOS/EUFOREA framework, which recommends multidimensional criteria (i.e., symptoms, rescue medication use and endoscopic appearance) for assessing disease control but also acknowledges the variability and limited objectivity of symptom-based measures [7,8,23]. Endoscopy was therefore used as the sole criterion to enhance reproducibility and minimize subjectivity.

Data sources and measurement

QoL was assessed using the SNOT-22 questionnaire, which rates individual items on a 6-point scale (0=no issue, 5=most severe issue), with total scores ranging from 0–110 to quantify symptom severity [24]. Endoscopic assessment included the NPS, scoring each nostril separately on a scale of 0 to 4 based on the presence and extent of nasal polyps within the nasal cavity, and the MLK system, which scores from 0 to 12 (accounting for polyps, edema and nasal discharge) [25,26]. Radiological findings were assessed using the LM system [27]. In all outcome measures, higher scores indicate more severe bilateral disease. Baseline endoscopic scores were recorded in the preoperative consultation and verified intraoperatively, then reviewed at follow-up by the same expert rhinologists, with any discrepancies solved through consensus.

Postoperative care was standardized across all groups. Absorbable nasal packing (typically NasoPore® or Spongostan®) was applied to the surgical field, followed by non-absorbable packing (RapidRhino™), which was removed 48 hours after ESS, in line with the institutional routine protocol during the study period. Thereafter, nasal rinses with seawater or saline were initiated three times daily. In cases involving endoscopic septoplasty, silicone sheets were used for at least 3 weeks. Medical treatment, including intranasal corticosteroids in addition to nasal irrigations, was resumed three weeks post-surgery. Adherence to prescribed therapy was monitored and reviewed by otolaryngology nurses at each follow-up visit.

Bias

Potential sources of bias related to patient selection and baseline disease severity were carefully addressed using standardized recruitment and the application of advanced statistical methods. Thus, multiple regression models and subgroup analyses were performed to account for potential confounders and to better estimate the relationship between surgical intervention and clinical outcomes in CRSwNP, while also generating hypotheses regarding the association between surgical extent and specific clinical phenotypes. Moreover, although the surgical scope was assigned according to predefined criteria, a degree of operator dependent bias remains inherent to surgical practice, stemming not only from the single center setting but also from intraoperative case specific findings and surgeon experience [13,14]. To strengthen methodological rigor and ensure comprehensive reporting, the STROBE checklist was applied (Table S2).

Study size

No formal a priori sample-size calculation was performed, as all consecutive eligible cases within the study period were included to ensure complete population coverage and minimize bias. Given that this is the first study to evaluate treatment escalation in CRSwNP patients, no reliable effect size was available for an a priori estimate. To assess sample adequacy, a post hoc statistical power analysis was carried out using the effect sizes derived from the multivariable models. In this analysis, the significance level was fixed at $\alpha = 0.05$, and the minimum number of events and patients required to detect the observed effects with 95% probability was calculated, confirming that the observed sample exceeded these requirements.

Quantitative variables

Quantitative variables were summarized as means and standard deviations or medians and interquartile ranges (IQR), according to data distribution. Normality of numerical variables was evaluated via the central limit theorem and confirmed using the Kolmogorov-Smirnov or Shapiro-Wilk tests, depending on the sample size in each subgroup, and equality of variances was verified with Levene's test. For comparative and multivariable analyses, variables were modeled as continuous or categorized when clinically justified to improve interpretability, following established thresholds within the CRSwNP framework [8,18,19].

Statistical analysis

Patient demographics, baseline characteristics and outcome measures were assessed using descriptive statistics. For each surgical group, comparisons were made either at the point of treatment intensification (for those who required it) or at the end of follow-up (for those who did not meet criteria for escalation), rather than to assess changes after intensification. Nu-

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Table 1. Distribution of demographic variables, medical history, endoscopic and radiologic scores, allergy studies and QoL in surgical groups before surgery.

	Type 1 (n = 57) N (%)	Type 2 (n = 43) N (%)	Type 3 (n= 45) N (%)	Type 4 (n = 27) N (%)
Gender (men)	37 (64.9)	33 (76.7)	30 (66.7)	16 (59.3)
Age ($\mu_x \pm$ SD)	52.3 ± 12.5	52.6 ± 12.8	49.6 ± 14.1	51.9 ± 12.5
Asthmatics	14 (24.6)	21 (48.8)	27 (60.0)	17 (63.0)
N-ERD	2 (3.5)	13 (30.2)	8 (17.8)	10 (37.0)
Proven allergic sensitization	31 (54.4)	24 (55.8)	25 (55.6)	14 (51.9)
Previous ESS 0 ESS 1 ESS ≥ 2 ESS	 0 (100) - -	 16 (37.2) 27 (62.8) 0	 29 (64.4) 1 (33.3) 15 (2.2)	 13 (48.1) 0 (0) 14 (51.9)
Smoker	11 (19.3)	7 (16.3)	6 (13.3)	4 (14.8)
≥1 cycles of SCS in the pre – surgery year	21 (36.8)	22 (51.2)	26 (57.8)	14 (51.9)
Nasal polyps score ($\mu_x \pm$ SD)	4.4 ± 1.7	5.1 ± 2.0	5.7 ± 1.5	5.8 ± 1.3
MLK scale (add of both nostrils) ($\mu_x \pm$ SD)	7.7 ± 2.1	8.8 ± 1.6	9.1 ± 2.0	8.9 ± 1.8
Lund – Mackay scale ($\mu_x \pm$ SD)	13.5 ± 4.2	14.8 ± 5.4	17.8 ± 5.1	19.7 ± 4.0
Eosinophils in peripheral blood > 300cells/μL	34 (59.6)	27 (62.8)	30 (66.7)	16 (59.3)
Total IgE > 100 UI/mL	27 (47.4)	23 (53.5)	34 (75.6)	23 (85.2)
Baseline SNOT–22 ($\mu_x \pm$ SD)	55.4 ± 22.1	62.2 ± 24.8	69.9 ± 17.8	76.5 ± 24.4
Baseline item 21 (smell) of SNOT–22 ($\mu_x \pm$ SD)	3.4 ± 1.7	4.0 ± 1.3	4.7 ± 0.7	4.6 ± 0.7

Abbreviations: μ_x: arithmetic average, Ig: immunoglobulin, MLK: modified Lund Kennedy, N-ERD: NSAID exacerbated respiratory disease, SCS: systemic corticosteroids, SD: standard deviation, SNOT-22: Sinonasal Outcome test–22.

merical outcomes were compared using independent samples t-tests, and results were displayed as violin plots with overlaid boxplots illustrating both the distribution and estimated probability density of the data, as well as median and IQR.

A multiple logistic regression model (enter method) was used to assess the impact of surgical extent on treatment escalation. To account for potential confounding effects, all clinically relevant covariates identified were included simultaneously, comprising demographic (gender, age) and clinical factors (smoking, asthma, N-ERD, atopy, previous ESS, blood eosinophilia, total serum IgE, SCS cycles and smell disturbance), as well as baseline endoscopic, radiologic and QoL measures. Odds ratios (OR), 95% confidence intervals (CI) and p-values were calculated to estimate escalation risk within three years post-surgery. An additional exploratory stepwise logistic regression (forward and backward) was performed, allowing the identification of the subset of variables that preserved the strongest independent association with treatment escalation.

A complementary descriptive and multivariate survival analysis was conducted to assess time to the need for treatment escalation based on the ESS extension. Kaplan-Meier survival curves represented the data by surgery type and were compared using the log-rank test. Cox regression models were employed to analyze the effect of ESS type on time to treatment escalation, incorporating all variables described in the previous multivariate models and adjusting for relevant covariates identified during model building. The model quantified the probability of the event of interest through the estimation of the hazard ratio (HR) and 95% CIs. To enhance the robustness, stratified Cox analyses were performed, dividing patients according to clinically relevant variables, such as age, gender, smoking, asthma, N-ERD, atopy, history of previous ESS, serum eosinophilia and total IgE. The assumptions of the Cox model (proportional hazards assumption) were assessed using the Schoenfeld residuals test and inspection of residuals.

For multivariate analyses, surgical extent was dichotomized into mucosal-sparing (t1-t2) and extensive mucosal resection (t3-t4), a distinction supported by clinical evidence showing superior outcomes with more extensive procedures [17,21,28] and by histological and ultrastructural studies demonstrating distinct patterns of epithelial regeneration and inflammatory resolution after greater mucosal removal [29–31]. This grouping strategy also enhanced statistical power and ensured consistency across analytic models. All statistical tests were conducted using IBM SPSS-Statistics v28 and p-values <0.05 were considered statistically significant.

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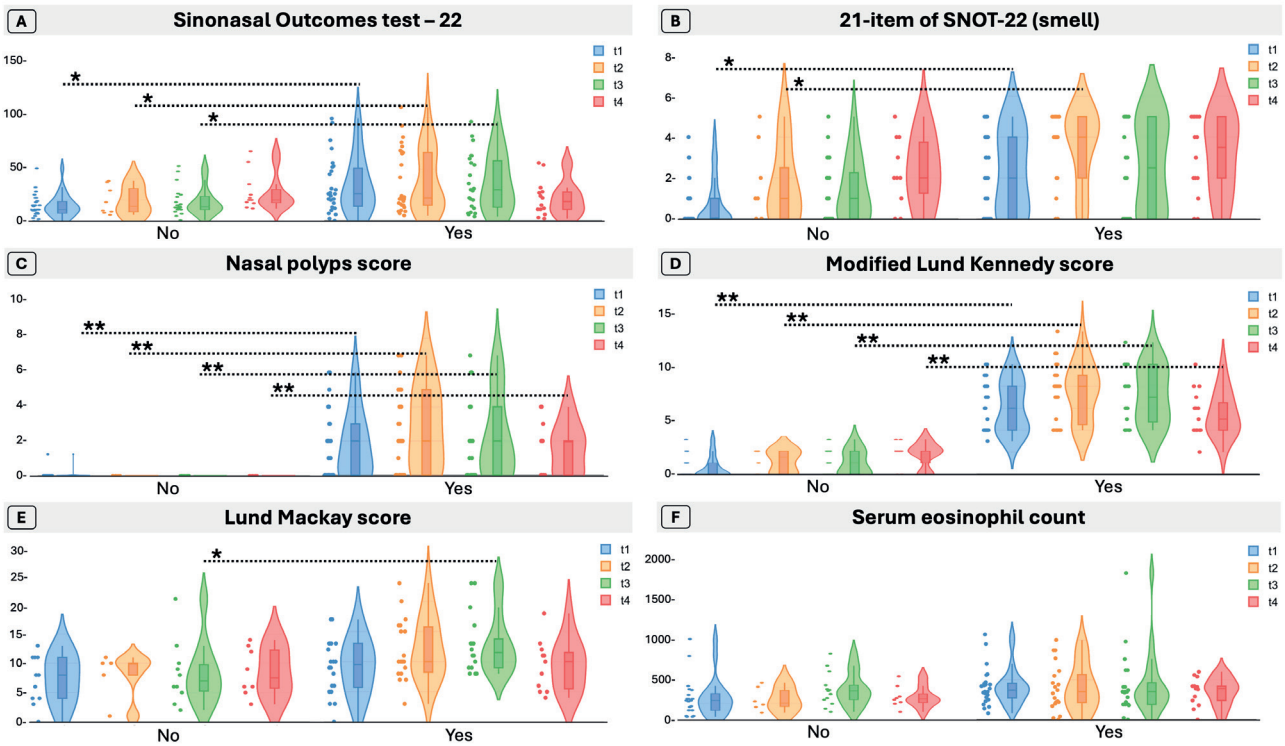

Figure 1. Violin and box plots illustrate symptom burden distribution, endoscopic measures, radiologic score and eosinophilia across LOEM surgical subgroups, comparing patients with and without need of treatment intensification. Width of each violin reflects the kernel density estimate, with wider sections indicating more frequent values. Box plots are embedded within each violin to display the median (horizontal line), IQR (box edges) and the data spread (whiskers). Each ESS type is represented by a distinct color: t1 (blue), t2 (orange), t3 (green) and type 4 (red). Individual points next to each violin represent specific values of each patient. *p<0.05, **p<0.001.

Results

Participants and descriptive data

Table 1 presents the distribution of baseline variables for 172 patients across the surgical groups. Age, gender, smoking status, atopy and serum eosinophilia were similar across LOEM types. By contrast, indices of disease burden increased from t1 to t4 procedures: asthma prevalence rose from 24.6% to 63.0%, N-ERD from 3.5% to 37.0% and prior ESS from none to about half of patients. Preoperative SCS and total IgE >100 UI/mL also increased with surgical extent. Endoscopic and radiologic scores rose steadily, accompanied by a clinically relevant growth in baseline SNOT-22 scores, including the smell item, from 55.4 to 76.5 points.

Treatment escalation and disease outcomes

Using endoscopic criteria to define escalation, patients who were eligible for therapeutic intensification showed significantly higher SNOT-22 scores compared to those who did not ($p < 0.001$). The distribution of scores in the intensification group was broader and skewed toward higher values, with a mean score of 43.8 ± 19.4 (range: 21–99). In contrast, patients without intensification needs had lower and more tightly clustered scores (SNOT-22 mean value = 18.4 ± 3.7 points). These differences remained consistent when analyzing each surgical group individually, except for the t4 ESS group ($p = 0.471$), as shown in the violin plot with overlaid boxplots (Figure 1). Differences in the determination of olfactory disturbance (item 21 of the SNOT-22 questionnaire) were maintained for the surgical subgroups t1 ($p = 0.011$) and t2 ($p = 0.036$). As expected, based on the therapeutic escalation criteria used, differences in endoscopic scores were also observed across all surgical groups. No differences were found in radiologic scores or in the inflammatory burden, as measured by serum eosinophilia (Figure 1).

ESS extension and risk of treatment escalation

Multivariate logistic regression identified the type of ESS and baseline disease severity as significant predictors of treatment escalation (Table 2), while comorbidities and other measures of disease burden showed no significant influence. Thus, compared to limited surgical approaches (t1-t2), patients who underwent t3-t4 ESS had a significantly lower likelihood of requiring therapeutic escalation (OR = 0.26, 95%CI: 0.08-0.83, $p = 0.014$). This result was confirmed with the stepwise multivariate model (OR = 0.30, 95%CI: 0.09-0.76, $p = 0.014$). In addition, a trend toward increased odds of intensification was observed in patients with severe baseline SNOT-22 scores, although the association did

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Table 2. Crude and adjusted odds ratio (OR) and 95% confidence interval (CI) for the need for therapeutic intensification, according to the full multivariable model (enter) and the final stepwise model.

	Adjusted OR (full model)*1	CI 95%	p value	Adjusted OR (exploratory model)*2	CI 95%	p value
Male (gender)	0.60	(0.20 to 1.81)	0.366			
Age	0.99	(0.94 to 1.05)	0.298			
Asthma	1.35	(0.33 to 5.49)	0.677			
N-ERD	1.50	(0.32 to 7.09)	0.609			
Proven allergic sensitization	1.18	(0.35 to 4.03)	0.788			
Previous ESS	2.59	(0.82 to 8.18)	0.106	2.62*3	(0.87 to 7.3)	0.088
Smoker	0.68	(0.13 to 3.55)	0.641			
≥1 cycles of SCS in the pre-ESS year	1.02	(0.31 to 4.03)	0.788			
Baseline NPS	1.08	(0.72 to 1.61)	0.727			
Baseline MLK scale	0.82	(0.58 to 1.16)	0.255			
Baseline LM scale	1.01	(0.88 to 1.16)	0.853			
Eosinophils in peripheral blood	1.78	(0.37 to 8.51)	0.468			
Total IgE	1.00	(0.99 to 1.00)	0.385			
Severe baseline SNOT–22	2.72	(0.73 to 10.10)	0.134	3.05*4	(0.93 to 9.97)	0.065
Baseline SNOT-22 – item 21 (smell)	1.53	(0.84 to 2.78)	0.165			
Radical ESS (t3-t4) (surgical extent)	0.26	(0.08 to 0.83)	0.014	0.30*5	(0.09 to 0.76)	0.014

*1 Multivariable logistic regression (enter method) including all clinically relevant variables identified a priori, ensuring mutual adjustment for potential confounders. *2 Exploratory stepwise multiple logistic regression, retaining only variables that remained in the final step when applying a variable selection algorithm based on statistical significance ($p < 0.15$). *3 Adjusted for significant independent factors (type of surgery, severe baseline SNOT-22) according to stepwise multiple logistic models. *4 Adjusted for significant independent factors (type of surgery, previous ESS) according to stepwise multiple logistic models. *5 Adjusted for significant independent factors (severe baseline SNOT-22, previous ESS) according to stepwise multiple logistic models. Abbreviations: ESS: endoscopic sinus surgery, Ig: immunoglobulin, LM: Lund-Mackay, MLK: modified Lund-Kennedy, N-ERD: NSAID-exacerbated respiratory disease, NPS: nasal polyp score, SCS: systemic corticosteroids, SNOT-22: Sinonasal Outcomes test–22.

not reach statistical significance (OR = 3.05, 95%CI: 0.93–9.97, p = 0.065). By contrast, previous ESS showed a non-significant trend (OR = 2.62, 95%CI: 0.87-7.3, p = 0.088).

Time to therapeutic escalation: survival analysis

Figure 2 presents the Kaplan-Meier survival analysis assessing the time to therapeutic escalation across ESS types. Surgeries classified as t3 and t4 demonstrated longer survival time, whereas t1 and t2 showed rapid decline. The log-rank test confirmed significant differences in survival distributions among groups (p = 0.009). Post hoc comparisons revealed persistent differences between t4 and the t1-t2 surgeries (p = 0.022, p = 0.010), as well as between t3 and t2 (p = 0.028). No other pairwise comparisons reached statistical significance.

Cox regression analysis (Figure 3) showed a significantly lower risk of therapeutic escalation over time in patients undergoing radical ESS (t3-t4) compared to functional mucosal ESS (t1-t2) (HR = 0.46, 95%CI: 0.24–0.87, p = 0.017). This effect was modulated by prior ESS (p = 0.023). Stratified analysis showed no statistically significant subgroup differences but suggested trends. Thus, more extensive ESS was associated with reduced escalation in patients over 45 years (HR = 0.36, 95%CI: 0.15–0.82), males (HR = 0.40, 95%CI: 0.17–0.95), non-smokers (HR = 0.48, 95%CI: 0.26–0.91) and atopic (HR = 0.34, 95%CI: 0.13–0.90). No significant differences were observed based on asthma or N-ERD status. In both groups of patients, with and without prior ESS, t3-t4 surgeries were associated with reduced escalation risk (HR = 0.13 and 0.30, respectively). Among biomarker-defined groups, a lower risk was observed in those with eosinophils >300 cells/µL (HR = 0.41, 95%CI: 0.19–0.88) and IgE ≤100 IU/mL (HR = 0.03, 95%CI: 0.0–0.45).

Discussion

Key results

This study is the first to comprehensively evaluate the impact of ESS extent on the need for subsequent treatment escalation in CRSwNP patients. Our findings suggest that, given the endoscopic thresholds used, patients requiring intensification had

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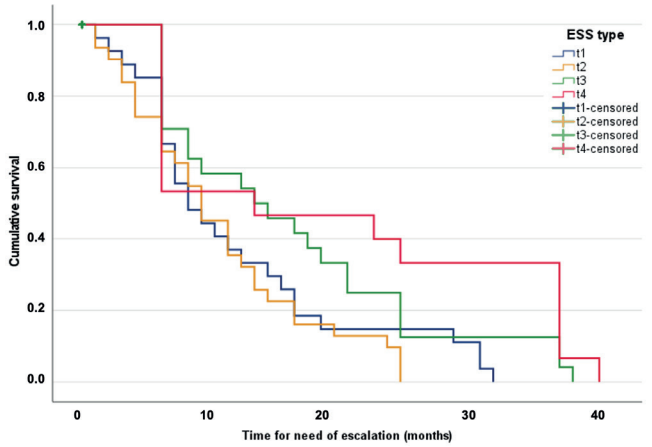

	Overall	t1-t2	t1-t3	t1-t4	t2-t3	t2-t4	t3-t4
Log-rank test (p value)	0.009	0.396	0.093	0.022	0.028	0.010	0.270

Figure 2. Kaplan-Meier survival analysis of therapeutic escalation. The x-axis represents the time to intensification in months, while the y-axis shows the cumulative survival, where higher values indicate a longer duration before the need for additional treatment. Each ESS type is represented by a distinct color: t1 (blue), t2 (orange), t3 (green) and type 4 (red). Censored observations are marked with crosses corresponding to each group's color. P values for the overall log rank test and in pairwise comparisons are shown in the table at the bottom.

greater disease burden than those who did not. Moreover, we observed that more radical mucosal ESS (t3-t4) were associated with a reduced risk of escalation over time, as confirmed by multivariate regression and survival analyses.

Implications of treatment escalation and disease burden

Several studies have shown that endoscopic improvement alone does not ensure effective symptom relief, highlighting discrepancies between clinician- and patient-centered definitions of control [6,7,32,33]. While recent efforts have proposed numerical endoscopic thresholds to better define uncontrolled disease [11], relying exclusively on examiner-dependent findings may underestimate the true disease burden and lead to overtreatment. Curiously, the results revealed that patients who required therapy escalation also had poorer QoL, reflected by a mean SNOT-22 score of 43.8, consistent across surgical groups (Figure 1A). These findings align with clinical guidelines, where scores above forty denote impaired QoL [7,8]. Additionally, worse smell scores were also recorded among patients who were candidates for therapeutic escalation, especially in those who had undergone t1-t2 surgeries (Figure 1B). However, the discrepancies regarding the association between surgical extent and olfactory disturbance, as well as the low reliability of this tool (item-21) for assessing smell, highlight the need for more comprehensive studies that include validated olfactory tests [34,35]. These insights may strengthen the relevance of the endoscopic thresholds and, together with other aspects such as the minimal clinically important difference [36], help lay the foundation for standardized criteria for CRSwNP control.

On the other hand, even though the expected differences in endoscopic scores due to the CRSwNP control criteria used, our analysis showed that the largest differences were observed in the NPS scale, regardless of the surgery type (Figure 1C), reinforcing the previously observed relationship between polyp size and poorer symptom control [32,37,38]. Although disparities were also observed in the MLK scale, its grading system's reliance on polyp growth may have contributed to an overestimation of the effect (Figure 1D). Nonetheless, this suggests that mucosal edema and secretions, in the absence of polyps, may not adequately reflect disease activity [11,39].

In contrast, other objective measures of disease such as radiologic findings and serum eosinophilia showed minimal differences among candidates for treatment escalation (Figure 1E–F). This lack of significance may be explained by the inherent limitations of radiologic scoring [40], as well as the inadequate definition of the relationship between blood eosinophilia and disease activity [41,42]. These findings suggest that such measures might be excluded as useful criteria in a more precise definition of disease control in CRSwNP patients.

Role of ESS extension in predicting treatment escalation

In addition, multivariate logistic analysis identified surgical extent and baseline symptom severity as independent predictors of treatment escalation, while comorbidities and other inflammatory biomarkers showed no significant association (Table 2). Patients who underwent t3-t4 surgeries had a markedly lower likelihood of requiring further interventions, hinting that not only surgical extension, but also more aggressive mucosal procedures may be associated with better disease control in the medium to long term [43–45], even in patients with poor-prognosis phenotypes [17,46]. Thus, although functional approaches (i.e., t1-t2) encompassed a wide range of techniques, from localized access to full-house functional ESS, partial mucosal resection remained consistent across these procedures, which does not align with the current surgical management based on the mucosal concept of CRSwNP [29,30]. In contrast, this protective effect observed with radical mucosal approaches may reflect the profound mucosal remodeling and attenuation of persistent inflammatory activity induced by these procedures, as evidenced by histological studies showing that extensive ESS promotes the development of neomucosa closely resembling the structure of healthy sinonasal epithelium [31,47]. However, further research is needed, especially as the expanding landscape of biologic therapies may gradually alter surgical indications. Moreover, a trend toward increased likelihood of treatment escalation was observed in patients with higher baseline SNOT-22 scores ($p = 0.065$). This finding still challenges the notion, suggested in earlier studies, that worse baseline QoL is consistently associa-

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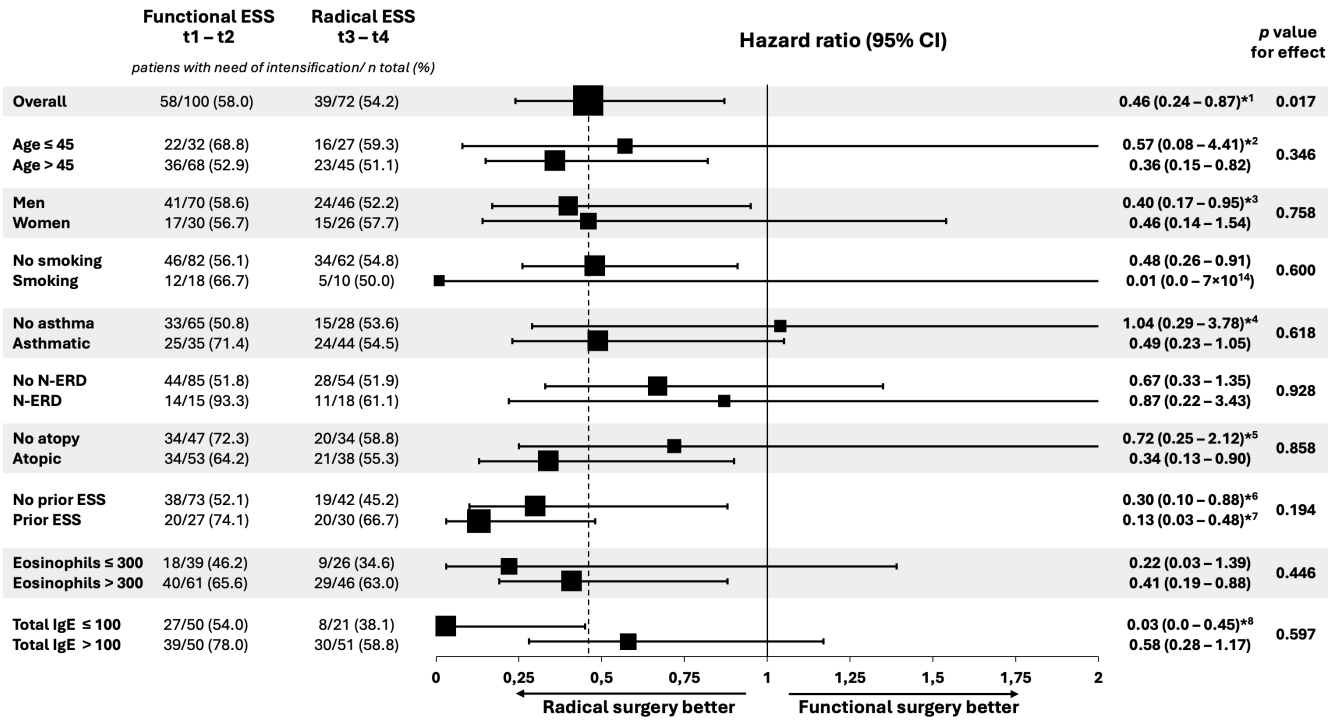

Figure 3. Cox regression analysis of the need for treatment escalation in CRSwNP patients based on the extent of ESS. The hazard ratio (HR) and 95% confidence interval (CI) for each subgroup are displayed. HR < 1 indicates a lower risk of escalation with radical (t3–t4) compared to functional ESS (t1–t2). The size of the squares represents the weight of each subgroup in the analysis. Significant independent factors for fitting multiple Cox regression models: *1 Prior ESS; *2 Gender, smoking, asthma, atopy, prior ESS; *3 Smoking; *4 Atopy; *5 Smoking; *6 Age, gender, asthma; *7 Smoking, asthma; *8 Atopy.

ted with greater postoperative improvement [17,36]. This may be attributed to differences in study populations, follow-up periods after ESS, or simply the control criteria applied.

Time to therapeutic escalation: interpretation of survival analysis findings

Survival curves further reinforced the role of ESS extent in disease control. Higher-grade procedures (i.e., t3-t4 surgeries) were associated with longer periods free from requiring treatment escalation (p = 0.009) (Figure 2). Specifically, in the t4 group, the more pronounced curve steps likely reflect the smaller cohort size and event distribution rather than a diminished effect. Nevertheless, these findings support the possibility of a sustained benefit of radical ESS, not only in reducing the overall risk of escalation but also in prolonging the time to subsequent interventions. Evidence from long-term follow-ups consistently reinforces this observation [44,48], highlighting its important implications for therapeutic planning, such as determining the timing for reoperation or biologic therapy introduction.

Although subgroup stratification introduced certain challenges, the multivariate analysis identified consistent and clinically meaningful patterns (Figure 3). Older patients appeared to benefit particularly from extensive surgery (HR = 0.36; 95%CI: 0.15-0.82), possibly due to a combination of reduced regenerative capacity and age-related immune modulation. In this context, the immunomodulatory effect of extensive surgery may mitigate elevated mucosal TNF-α expression by promoting type 1 immune pathways, thereby limiting chronic inflammation [49,50]. Similarly, these approaches showed a protective trend in poor-prognosis inflammatory phenotypes, reaching significance only in atopic patients (HR = 0.34; 95%CI: 0.13-0.90), likely reflecting both small subgroup sizes and the benefit of extensive mucosal removal even with marked immunologic dysregulation [17,43,45]. The protective effect was even greater in revision cases (HR = 0.13; 95%CI: 0.03-0.48), possibly due to the targeted removal of anatomical remnants and all mucosae, including macroscopically normal areas harboring ongoing inflammation and epithelial remodeling [12,28,30]. Likewise, patients with elevated eosinophil counts (>300 cells/μL) benefited from radical ESS (HR = 0.41; 95%CI: 0.19-0.88), suggesting reduced escalation risk under these surgical approaches even in high T2-inflammation patients. Ultimately, while other subgroups did not reach statistical significance, most HRs consistently favored radical surgery across most clinical scenarios. Nonetheless, the limited sample size in certain subgroups, such as N-ERD or smokers, calls for cautious interpretation and further studies.

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Limitations

This study presents some limitations that should be considered. Despite the identification and mitigation of potential sources of bias through predefined surgical criteria and multivariate analyses, the retrospective non-randomized and single-center design may still limit causal inference. Furthermore, although multiple postoperative outcomes (e.g., QoL, smell, endoscopy, radiology, serum eosinophilia) were compared between patients with and without need for escalation (Figure 1), the study was not designed to assess longitudinal changes after intensification. To address this notable limitation, future prospective studies specifically designed to evaluate post-escalation outcomes merit investigation.

Another limitation relates to the isolated use of endoscopic criteria to define treatment intensification, which may not fully capture the patient's symptomatic burden. These criteria, recently proposed and derived from an expert consensus, provide a standardized approach but also carry inherent limitations and remain subject to interpretation and inter-observer variability [8,19]. Moreover, in real-world clinical practice, treatment escalation decisions are often shared between physician and patient, potentially introducing additional variation that could not be fully captured in our analysis. This limitation was partially addressed by analyzing the distribution of outcome measures between patients who were candidates and non-candidates for therapeutic escalation, as well as by employing multivariate models.

Interpretation

This study provides emerging evidence suggesting an association between the extent of surgery, as defined by the LOEM classification, and both the timing and likelihood of therapeutic escalation in CRSwNP patients. These findings should be interpreted cautiously, given the retrospective design and potential residual confounding despite statistical adjustments. The observed tendency toward a reduced risk of escalation and prolonged disease control in patients undergoing more extensive mucosal surgery suggests a clinical benefit consistent with previous reports linking broader surgical access and mucosal remodeling to improved outcomes. Specifically, patients undergoing more extensive mucosal surgeries (t3-t4) exhibited a trend toward more stable disease, particularly within certain phenotypic subgroups, which may support the value of tailoring surgical strategies to individual patient profiles within precision medicine frameworks.

Generalizability

Although the study design may limit external validity, the detailed description of surgical techniques using the LOEM system, together with the perioperative protocols and follow-up strategies applied in this cohort, closely align with current recommendations [8,18,19], facilitating comparability with other centers. To further enhance external validity, future research should include multicenter prospective cohorts, external validation of LOEM-based stratification, and integration of real-world data to confirm the generalizability of these findings across diverse clinical settings.

Conclusion

The observed association between endoscopic findings and symptom burden highlights the potential clinical value of endoscopic thresholds as practical markers for monitoring CRSwNP status. In this cohort, more extensive mucosal surgeries (t3-t4) were associated with a lower risk and a longer time to therapeutic escalation. While the current analysis may inform more nuanced clinical practice patterns, further prospective, large-scale studies are warranted to validate these results and improve individualized treatment algorithms aimed at optimizing long-term disease control.

Author contributions

Conception: MCC, DMJ, RML, SSG. Design: MCC, DMJ, RML, AC. Supervision: MCC, DMJ, IA, SSG. Resource: DMJ, RML, IA, SGS. Materials: MCC, DMJ, RML, MGG, SSG. Data collection and/or processing: MCC, DMJ. Analysis and/or interpretation: MCC, DMJ, RML. Literature search: MCC, DMJ, RML. Writing: MCC, DMJ, RML, IA. Critical reviews: MCC, DMJ, RML, AC, IA, SSG.

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Conflict of interest

The authors report no conflict of interest.

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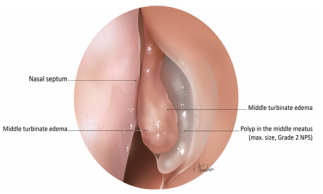
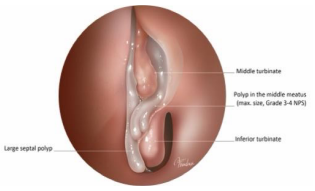
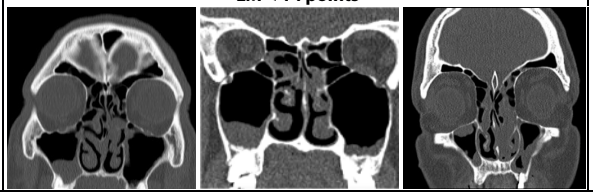
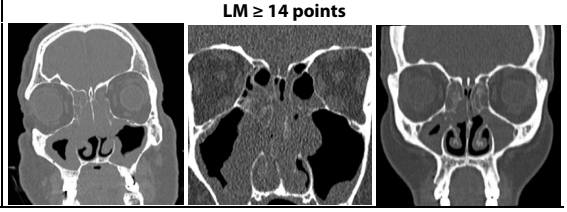
SUPPLEMENTARY MATERIAL

Table S1. Standards for surgical extension indication.

	Type of surgery	
	Limited ESS (t1 – t2)	**Extended ESS (t3 – t4)**
Asthma[1,2]	Well controlled: No recent exacerbations, stable symptoms and adequate control with low-to-moderate maintenance therapy	Uncontrolled: Recurrent exacerbations or ongoing symptoms despite high-intensity therapy
N-ERD[3,4]	Mild to moderate asthma with upper airway symptoms, blood eosinophilia and low healthcare use	Severe or poorly controlled asthma, with frequent exacerbations and airway obstruction. Increased need for systemic steroids and hospital visits.
Previous ESS	0 – 1*	≥ 2
Endoscopic image		
CT–scan score[5]	**LM < 14 points** 	**LM ≥ 14 points** 

*t1 surgeries were not indicated in patients with any prior surgery. Polypectomy, balloon dilations and any other procedures that did not involve resection of bony structures were not considered prior surgeries.

Abbreviations: CRS: chronic rhinosinusitis, CRSsNP: chronic rhinosinusitis without nasal polyps, CRSwNP: chronic rhinosinusitis with nasal polyps, CT: computed tomography, ESS: endoscopic sinus surgery, LM: Lund Mackay score, N-ERD: NSAID-exacerbated respiratory disease

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Table S2. STROBE Statement—checklist of items that should be included in reports of observational studies [1].

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1-2	Title and Abstract methods section
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2	Abstract methods and results sections
Introduction				
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4	Paragraphs 1-3
Objectives	3	State specific objectives, including any prespecified hypotheses	4	Paragraph 4
Methods				
Study design	4	Present key elements of study design early in the paper	4	Study design subheading
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4	Setting subheading
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4	Participants subheading
		(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed	NA	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6	Variables subheading
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6	Data sources and measurement subheading
Bias	9	Describe any efforts to address potential sources of bias	7	Bias subheading
Study size	10	Explain how the study size was arrived at	7	Study size subheading
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8	Quantitative variables subheading
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8	Statistical analysis - paragraphs 13-14 of methods section
		(b) Describe any methods used to examine subgroups and interactions	8-9	Statistical analysis - paragraph 15 of methods section
		(c) Explain how missing data were addressed	NA	Not applicable (i.e., only patients with complete data of predefined variables were included
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed	NA	Not applicable (i.e., only individuals "who met full eligibility criteria and completed the predefined follow-up protocol", were selected)
		(e) Describe any sensitivity analyses	8-9	Statistical analysis - paragraphs 14-15 of methods section
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9	Participants and descriptive data - paragraph 1 of results section and Table 1
		(b) Give reasons for non-participation at each stage	NA	Not applicable (i.e., including only individuals who […] completed the predefined follow-up protocol)
		(c) Consider use of a flow diagram	NA	Not applicable

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	Item No.	Recommendation	Page No.	Relevant text from manuscript
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	-	Tables 1 and 2; Figure 1
		(b) Indicate number of participants with missing data for each variable of interest	-	Table 1
		(c) Cohort study—Summarise follow-up time (eg, average and total amount)	NA	Not applicable (i.e., including only individuals who […] completed the predefined follow-up protocol)
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time	9-10	Treatment escalation and disease outcomes - paragraph 2 of results section; Figure 1
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10	ESS extension and risk of treatment escalation - paragraph 3 of results section; Table 2
		(b) Report category boundaries when continuous variables were categorized	-	Table 1 (e.g., eosinophila > 300cells/µL, IgE > 100 UI/mL); Figure 3
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-11	Time to therapeutic escalation: survival analysis - paragraphs 4-5 of results section; Figures 2 and 3
Discussion				
Key results	18	Summarise key results with reference to study objectives	11	Key results subheading
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15	Limitations - paragraphs 8-9 of discussion section
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-16	Interpretation subheading - paragraphs 10-11 of discussion section
Generalisability	21	Discuss the generalisability (external validity) of the study results	16	Generalizability - paragraph 12 of discussion section. Conclusion section.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21	Funding: "The authors have not received any funding"

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies. Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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