Baseline EPOS 2020 eligibility and real-world outcomes of dupilumab in CRSwNP: a longitudinal cohort study

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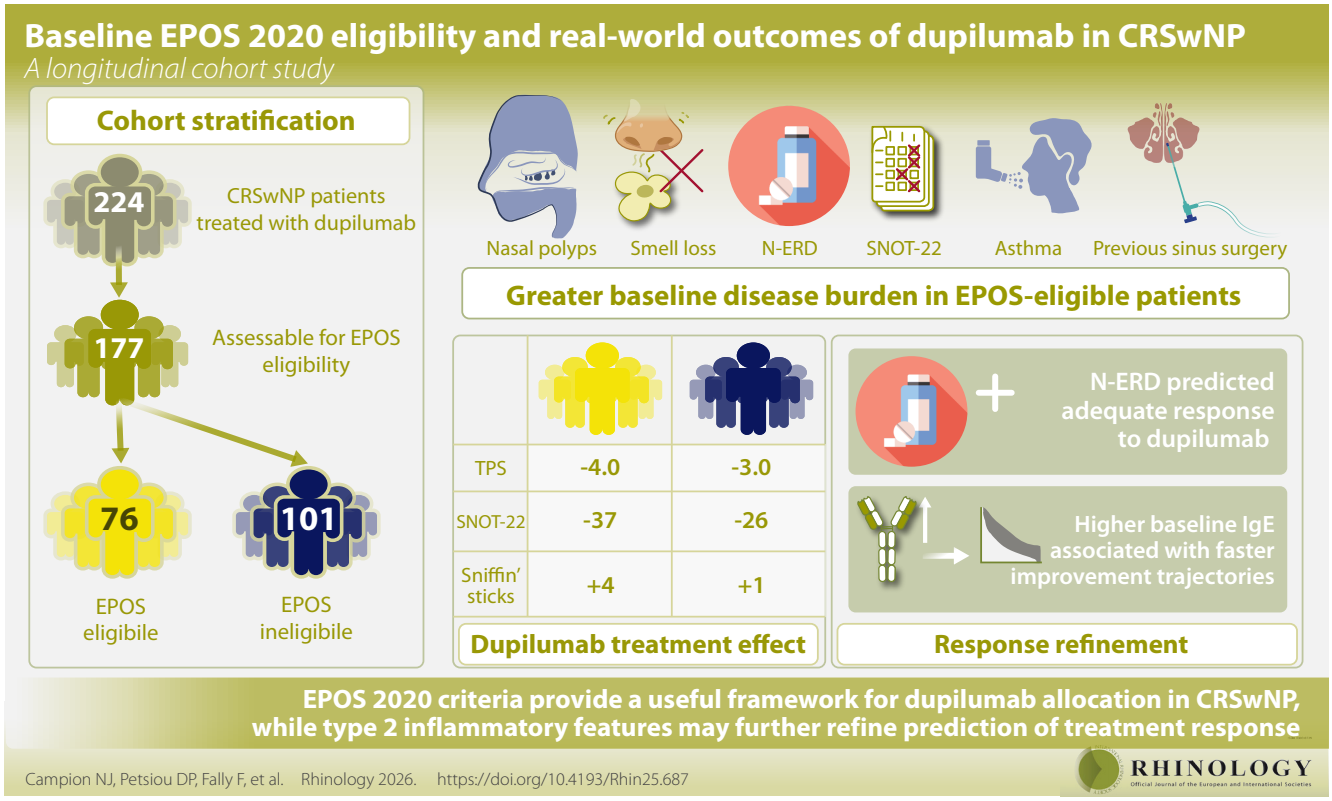

Abstract

Background: Chronic rhinosinusitis with nasal polyps (CRSwNP) is often a type 2–driven inflammatory disease that markedly impairs quality of life. Dupilumab offers major therapeutic benefit but at high cost, underscoring the need for accurate patient selection. EPOS2020 introduced indication criteria for biologic therapy, yet their real-world predictive validity remains underexplored. **Methods**: This study screened 224 CRSwNP patients treated with dupilumab between November 2019 and May 2025. Outcomes included Total Polyp Score (TPS), 22-item Sinonasal Outcome Test (SNOT-22), olfactory performance, and serum biomarkers. Patients were stratified into EPOS-eligible and ineligible groups based on EPOS2020 criteria, and responses were evaluated using minimal clinically important difference (MCID) thresholds and EPOS/EUFOREA response criteria. Predictors of adequate response were analyzed with logistic regression, and treatment trajectories with linear mixed-effects models. **Results**: EPOS2020 criteria could be assessed in 177 patients, of whom 76 met them at baseline. EPOS-eligible patients achieved greater improvements in TPS, SNOT-22, and olfaction, and were more likely to reach MCID for TPS. EPOS-eligible patients also had higher composite EPOS response scores, although "adequate EUFOREA response" rates did not differ. Non-steroidal anti-inflammatory drug exacerbated respiratory disease independently predicted adequate response, while higher baseline serum IgE was associated with faster improvement trajectories. **Conclusions**: EPOS2020 criteria provide an effective framework for dupilumab allocation, although markers of active type 2 inflammation may better predict response than categorical eligibility alone.

Key words: CRS, CRSwNP, chronic rhinosinusitis, dupilumab, EPOS 2020, biologics, EUFOREA

Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a persistent inflammatory condition of the paranasal sinuses [1]. It affects approximately 1-2% of the Western population [2-4] and has a significant impact on quality of life and healthcare utilization [5-8]. While intranasal corticosteroids and sinus surgery remain the standard therapeutic approaches for CRSwNP in routine practice, these strategies are not effective in all patients [9].

Recently, biologics have emerged as a transformative treatment option for CRSwNP, with dupilumab being one of the more efficacious agents [10-13]. However, the high cost of biologics underscores the need to identify patients who are most likely to benefit [14]. The European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS 2020) guideline was the first to provide widely adopted, specific indication criteria with defined cut-offs for biologic treatment in CRSwNP, serving as an international reference for clinical practice [15]. Although randomized controlled trials (RCTs) and real-world studies have already confirmed the efficacy of dupilumab across diverse populations [16-18], real-world validation of the EPOS 2020 indication criteria in terms of selecting the best patients for treatment is limited. While one real-world study reports larger improvements among EPOS 2020 indication criteria- eligible patients [19], studies including patients not meeting EPOS 2020 criteria have generally not stratified or compared outcomes according to EPOS 2020 status [20]. Furthermore, it is still unclear whether the EPOS 2020 criteria predict treatment response using both, absolute changes and clinically meaningful improvements, such as minimal clinically important difference (MCID) and the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA)/EPOS response criteria.

The present study aimed to evaluate the real-world outcomes of dupilumab in patients with CRSwNP, stratified according to the EPOS 2020 indication criteria. Specifically, we examined whether EPOS-defined eligibility for dupilumab predicts, not only absolute improvements, but also achievement of clinically meaningful benefits. In addition, we explored whether other baseline factors, such as nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (N-ERD), total IgE levels, and blood eosinophil counts, can further refine patient stratification and enhance prediction of treatment response beyond the current EPOS 2020 indication criteria framework.

Materials and methods

Study design and setting

This retrospective, single-center analysis was conducted at the Department of Otorhinolaryngology, Medical University of Vienna, General Hospital of Vienna, Austria. Ethical approval was granted by the institutional review board (EK: 1340/2025). The dataset included patients treated between November 2019 and May 2025.

Patient cohort and clinical protocol

A total of 224 patients diagnosed with CRSwNP according to EPOS 2020 diagnostic criteria had at least 1 baseline and 1 follow-up visit and therefore screened for inclusion. All began dupilumab treatment under European Medicines Agency (EMA) recommendations, which states that dupilumab is indicated as add-on therapy with intranasal corticosteroids for adults with severe CRSwNP for whom systemic corticosteroids and/or surgery do not provide adequate disease control [21]. All patients had at least one follow-up visit. The observation period extended up to 4.5 years, with outcomes modeled to 5 years. Follow-up generally occurred at baseline, 3, 6, and 12 months, and annually thereafter.

At each visit, clinicians documented demographic and clinical characteristics (age, sex, smoking, asthma (physician-diagnosed condition, confirmed by a respiratory specialist, requiring regular treatment with inhaled corticosteroids), allergy (positive history with documented use of antihistamines for symptom control), N-ERD (presence of: 1) asthma as defined above, 2) a documented history of hypersensitivity reactions to NSAIDs, and 3) evidence of chronic rhinosinusitis with nasal inflammation), and prior surgeries). Disease severity was assessed with the Total Polyp Score (TPS), olfactory function with the Sniffin' Sticks 16 Identification Test, and Patient Reported Outcome Measures (PROMs) with the 22-item Sinonasal Outcome Test (SNOT-22), Asthma Control Test (ACT), mini–Asthma Quality of Life Questionnaire (AQLQ), and aero-allergy Visual Analogue Scale (VAS, 10cm scale with higher values indicating higher disease burden). Annual blood samples were analyzed for IgE, Eosinophil Cationic Protein (ECP), and Absolute Eosinophil Count (AEC). All data were anonymized, stored on secure institutional servers, and curated by the Vienna Airway Lab team.

Statistical analysis

Baseline values were defined at treatment initiation (Day 0/ Baseline). For group comparisons patients were stratified by EPOS 2020 indication criteria as EPOS eligible or EPOS ineligible, and those with "Unknown" status due to missing data for group comparisons were excluded from the analysis.

EPOS 2020 indication criteria

Eligibility for biologic therapy was defined according to EPOS 2020/EUFOREA indication criteria [22]. Briefly to fulfill these criteria all patients are required to have had bilateral nasal polyps and prior endoscopic sinus surgery. In addition, they must fulfill at least three of the following five criteria:

1. Evidence of type 2 inflammation, defined as tissue eosinophils ≥10 per high-power field, blood eosinophils ≥150 cells/

μL, or total IgE ≥100 IU/mL
2. Need for systemic corticosteroids (≥2 courses per year or long term (>3 months) low dose steroids) or contraindication to systemic corticosteroids
3. Significantly impaired quality of life, defined as SNOT-22 ≥40
4. Significant loss of smell, defined as anosmia on smell testing
5. Comorbid diagnosis of asthma requiring regular inhaled corticosteroid therapy

Descriptive statistics and baseline comparisons

Categorical variables were reported as percentages and continuous variables as median and [Interquartile range, (IQR)], as distributions were non-normally distributed according to the Shapiro–Wilk test. Group comparisons were performed using chi-square or Fisher's exact tests for categorical variables and Mann–Whitney U tests for continuous variables. Rank-biserial correlation coefficients were calculated as non-parametric measures of effect size for Mann–Whitney U comparisons.

Treatment effect and MCID analyses

Treatment effects were evaluated by calculating delta changes (follow up visit – baseline visit) between baseline and the most recent clinical followup visit for each outcome (TPS, Sniffin' Sticks, SNOT-22, ACT, AQLQ, allergy VAS, IgE, ECP, AEC). Minimal clinically important differences (MCID), defined from published thresholds (Table S1), were used to determine patients fulfilling this measure of outcome.

EPOS/EUFOREA evaluation of response assessment

Response to biologic therapy was assessed based on the EPOS/EUFOREA criteria across five domains: nasal polyp size, systemic corticosteroid use, quality of life, olfaction, and comorbid asthma [19]. Each domain was evaluated as a binary outcome (improved vs not improved) using the following definitions:

- Nasal polyp size: reduction in total polyp score (TPS) compared with baseline
- Systemic corticosteroid use: reduction in the number of systemic corticosteroid courses during follow-up compared with the pre-treatment period
- Quality of life: improvement in SNOT-22 score compared with baseline
- Olfaction: improvement in Sniffin' Sticks score compared with baseline
- Comorbid asthma: improvement in asthma control (ACT score)

For each patient, only domains that were assessable at baseline were included. A domain was considered non-assessable if the patient did not exhibit the feature at baseline (e.g., no prior systemic steroid use, normosmia, absence of asthma). The total number of domains showing improvement was divided by the number of assessable domains to generate a normalised response score ranging from 0 to 1, where 1 indicates improvement in all assessable domains to allow comparison between patients with variable baseline assessable domains. For transparency 95 patients had all 5 criteria assessable at baseline, 64 had 4 assessable and 18 had 3.

"Adequate response" was defined according to EUFOREA criteria (TPS <4, nasal congestion score <2, CRS VAS <5 (only used to determine adequate response status, not used as a separate outcome measure), SNOT-22 <30, and no systemic steroid or surgical requirement) and assessed at 12 months (±60 days; closest to day 365) and at last available follow-up [23]. Baseline predictors of adequate response at last available follow-up were evaluated using multivariable logistic regression, including age, sex, smoking status, asthma, N-ERD, prior surgery, TPS, SNOT-22, total serum IgE, ECP, and AEC. Odds ratios (OR) with 95% confidence intervals (CI) were reported.

Longitudinal trajectory analysis

To assess longitudinal trajectories, linear mixed-effects models were fitted separately for each outcome (TPS, Sniffin' Sticks, SNOT-22, ACT, AQLQ, Allergy VAS, and serum biomarkers [IgE, ECP, AEC]). Models included baseline covariates, with biomarker variables log-transformed and continuous variables standardised. A patient-level random intercept was included to account for within-patient correlation from repeated measurements, and covariate × time interactions were used to evaluate whether baseline factors modified rates of change during treatment. Findings were interpreted with emphasis on effect sizes and consistency across outcomes but due to the retrospective design of this study should be interpreted as hypothesis generating rather than mechanistic insight.

Statistical software

All statistical analyses were performed using Python (v3.11.13; Python Software Foundation, Wilmington, DE, USA) with the packages pandas (v2.3.2), NumPy (v2.3.3), SciPy (v1.16.2), statsmodels (v0.14.5), and matplotlib (v3.10.6). Linear mixed-effects models were implemented in R (version 4.5.1; R Foundation for Statistical Computing, Vienna, Austria) using the lme4 package (v1.1-37), as this package provides established and validated functionality for mixed-effects modelling [24].

Results

Overview of study population and comparison groups

A total of 224 patients were assessed for study inclusion, of whom 76 (33.9%) fulfilled EPOS 2020 indication criteria, 101 (45.1%) did not. For 47 (21%) patients there was insufficient information to determine their EPOS 2020 eligibility criteria status. All further grouped analyses were restricted to the 177

Table 1. Baseline characteristics of the study cohort stratified by EPOS 2020 eligibility criteria.

Variable	EPOS eligible (n = 76)	EPOS ineligible (n = 101)	p-value
Demographics			
Male	57.9%	56.4%	1.000
Age (years)	48.5 [40.0–57.0]	47.0 [37.0–55.0]	0.392
Smoking	7.9%	8.9%	1.000
Length of Follow-up (years)	1.88 [1.15–3.21]	1.82 [0.85–3.00]	0.520
Comorbidities and disease burden			
Allergy	67.1%	54.5%	0.115
Asthma	80.3%	56.4%	<0.001
NERD	54.0%	29.7%	0.002
Number of previous ESS Surgeries	2.0 [1.0–3.0]	1.0 [0.0–2.0]	0.003
TPS	4.0 [4.0–6.0]	4.0 [2.0–6.0]	0.033
SNOT-22	55.0 [42.0–68.0]	40.0 [29.0–58.0]	<0.001
Sniffin' Sticks 16 identity Score	4.0 [3.0–6.0]	7.0 [4.0–11.0]	<0.001
ACT	19.0 [15.0–22.0]	21.0 [17.0–24.0]	0.142
AQLQ	78.0 [62.0–88.0]	84.0 [64.0–95.0]	0.160
Allergy VAS (10cm Scale)	6.9 [4.8–7.9]	6.6 [4.1–8.5]	0.997
Inflammatory biomarkers			
Total IgE (kU/L)	99.0 [51.0–388.0]	106.0 [40.0–328.0]	0.816
ECP (µg/L)	55.0 [34.0–88.0]	46.0 [23.0–71.0]	0.070
AEC ($\times 10^9$/L)	0.4 [0.3–0.5]	0.3 [0.2–0.4]	0.079

Demographic and clinical features were compared between patients who fulfilled EPOS indication criteria at baseline (EPOS Eligible) and those who did not (EPOS Ineligible). Categorical variables are reported as percentages and compared using chi-square or Fisher's exact test. Continuous variables are summarized as median [interquartile range] and compared using Mann–Whitney U tests. ACT = Asthma Control Test, AEC = Absolute Eosinophil Count, AQLQ = Asthma Quality of Life Questionnaire, ECP = Eosinophilic Cationic Protein, EPOS = European Position Paper on Rhinosinusitis and Nasal Polyps, ESS = Endoscopic Sinus Surgery Ig = Immunoglobin, NERD = NSAID Exacerbated Respiratory Disease, SNOT-22 = 22 item Sinonasal Outcome Test, TPS = Total Polyp Score, VAS = Visual Analogue Scale.

patients with clear EPOS categorization. Baseline characteristics of the included patients are presented in Table 1. Follow-up duration varied across the population. The median duration of follow-up from treatment initiation to last available visit was 1.85 years (IQR 0.94–3.15). Follow-up data were available for 177 patients within the first year, with progressively fewer patients contributing data at later timepoints (105 at 1–2 years, 59 at 2–3 years, 45 at 3–4 years, and 9 at 4–5 years). Compared with EPOS-ineligible patients, those fulfilling EPOS criteria demonstrated a higher baseline disease burden across multiple domains, including a greater number of prior sinus surgeries (2.0 [1.0–3.0] vs 1.0 [0.0–2.0]; p=0.003), and significantly higher rates of comorbid asthma (80.3% vs 56.4%; p<0.001) and N-ERD (54.0% vs 29.7%; p=0.002). They also exhibited worse disease severity, with higher SNOT-22 scores (55.0 [42.0–68.0] vs 40.0 [29.0–58.0]; p<0.001), poorer olfactory function (Sniffin' Sticks 16 Identity Score: 4.0 [3.0–6.0] vs 7.0 [4.0–11.0]; p<0.001), and slightly higher polyp scores (TPS 4.0 [4.0–6.0] vs 4.0 [2.0–6.0]; p=0.033). There were no significant differences between groups in other demographic factors, allergy status, asthma control (ACT), quality of life (AQLQ), allergy VAS, or inflammatory biomarkers (IgE, ECP, AEC) (Table 1).

Patients who fulfil EPOS criteria demonstrate greater improvements in polyp burden, symptoms, and olfaction

Delta change analysis (follow-up visit – baseline visit) was performed on the 177 patients with clear EPOS 2020 eligibility status according to the indication criteria for biologics (Table 2). Patients meeting EPOS indication criteria (EPOS eligible) showed significantly greater improvement in key clinical domains compared with non-eligible patients. Polyp burden reduction was more pronounced in the EPOS-eligible group (–4.0 [–5.0 to –2.8]) than in the EPOS-ineligible group (–3.0 [–4.0 to –1.0]; p<0.001, rank-biserial r=–0.33). Symptom burden measured by SNOT-22 improved by –37.0 [–53.0 to –20.3] in EPOS-eligible versus –26.0 [–40.0 to –10.8] in EPOS-ineligible patients (p=0.002, rank-bise-

Table 2. Median changes (Δ = last follow-up − baseline) in clinical and biomarker outcomes among patients stratified by EPOS 2020 eligibility at baseline.

Outcome	EPOS eligible (n=76)	EPOS ineligible (n=101)	p-value	Rank-biserial r
TPS	-4.0 [-5.0–-2.8]	-3.0 [-4.0–-1.0]	<0.001	-0.33
Sniffin' Sticks 16 Identity Score	4.0 [1.0–7.0]	1.0 [0.0–5.0]	0.009	0.24
SNOT-22	-37.5 [-53.0–-20.3]	-26.0 [-40.0–-10.8]	0.002	-0.29
ACT	3.0 [0.0–7.0]	3.0 [0.0–6.0]	0.780	0.04
AQLQ	15.0 [3.0–25.0]	11.8 [4.0–29.0]	0.972	0.00
Allergy VAS (10 cm scale)	1.5 [-0.5–3.8]	1.9 [0.4–4.7]	0.243	-0.17
Total IgE (kU/L)	-69.6 [-198.1–-37.8]	-69.5 [-252.2–-26.7]	0.664	-0.05
ECP (µg/L)	0.0 [-21.9–21.4]	-0.3 [-18.4–16.2]	0.968	-0.01
AEC ($\times 10^9$/L)	0.0 [-0.1–0.2]	0.0 [-0.1–0.2]	0.589	-0.08

Values represent the median change in each outcome variable. P-values are derived from the Mann–Whitney U test. Rank-biserial correlations are reported as non-parametric effect-size measures for between-group differences, where values closer to ±1 indicate greater group separation and values near 0 indicate minimal difference. Delta changes were calculated between baseline and the last recorded clinical follow-up visit for each patient; median follow-up duration was 1.85 years [0.94–3.15]. ACT = Asthma Control Test, AEC = Absolute Eosinophil Count, AQLQ = Asthma Quality of Life Questionnaire, ECP = Eosinophilic Cationic Protein, EPOS = European Position Paper on Rhinosinusitis and Nasal Polyps, Ig = Immunoglobin, SNOT-22 = 22-item Sinonasal Outcome Test, TPS = Total Polyp Score, VAS = Visual Analog Scale.e

Table 3. Proportion of patients achieving minimal clinically important difference (MCID) in key outcomes, stratified by EPOS 2020 eligibility at baseline.

Outcome	EPOS Eligible (n = 76)	EPOS Ineligible (n = 101)	p-value
TPS	98.7%	77.2%	<0.001
SNOT-22	89.6%	77.2%	0.056
Sniffin' Sticks 16 Identity Score	75.3%	65.3%	0.201
ACT	61.0%	51.5%	0.446
AQLQ	76.6%	86.1%	0.314
Allergy VAS (10cm Scale)	19.5%	14.9%	0.731

MCID was acquired by comparing baseline to last available follow-up across these key outcome measures, median follow-up duration was 1.85 years [0.94–3.15]. MCID thresholds were derived from established literature (Table S3).Statistical comparison between groups was performed using Fisher's Exact Test. ACT = Asthma Control Test, AQLQ = Asthma Quality of Life Questionnaire, EPOS = European Position Paper on Rhinosinusitis and Nasal Polyps, SNOT-22 = 22 item Sinonasal Outcome Test, TPS = Total Polyp Score, VAS = Visual Analogue Scale.

rial r=–0.29). Olfactory performance improved by +4.0 [1.0–7.0] versus +1.0 [0.0–5.0] (p=0.009, rank-biserial r=0.24). Other outcomes, including ACT, AQLQ, allergy VAS, and biomarker levels (IgE, ECP, and AEC), showed no significant between-group differences, though the direction of change consistently favored the EPOS-eligible group (Table 2).

EPOS-eligible patients more frequently achieve MCID in TPS and SNOT-22 and reach higher EPOS/EUFOREA evaluation of response scores

MCID analyses (for definitions for single items, please refer to Table S1) further supported these findings (Table 2). Nearly all EPOS-eligible patients achieved MCID in TPS (98.7%) compared with 77.2% of EPOS-ineligible patients (p<0.001). MCID in SNOT-22 was also more frequent in EPOS-eligible patients (89.6% vs 77.2%), nearly reaching significance (p=0.056). For other domains, Sniffin' Sticks, ACT, AQLQ, and allergy VAS, there were no statistically significant differences between groups.

We also assessed how the two groups performed in the EUFOREA evaluation of response criteria [22]. At the last recorded follow-up, patients who fulfilled EPOS 2020 indication criteria at baseline demonstrated significantly higher median response scores compared with those who did not (0.6 [0.6–0.8] vs 0.5 [0.4–0.6]; p < 0.001), data not shown.

Adequate response according to EUFOREA criteria shows no difference by EPOS eligibility

Adequate response to biologic therapy defined by EUFOREA criteria [23] was evaluated at both 12 months and the last available visit. At 12 months (±60 days), adequate response was observed in 68.0% of EPOS-eligible patients and 62.5% EPOS-ineligible patients, with no significant difference (p=0.791. At last available

Table 4. Baseline predictors of dupilumab treatment trajectory in disease specific outcomes identified using linear mixed-effects models.

Outcome	Predictor	Estimate	Std Error	t value	Interpretation
SNOT-22	Age	-5.36	1.64	-3.27	Older age associated with better baseline symptoms
	Sex (male)	-6.43	3.24	-1.98	Male sex associated with better baseline symptoms
	Total IgE	+5.03	1.05	4.79	Higher IgE associated with worse baseline symptoms
	Sex (male) × time	+0.48	0.14	3.41	Male sex associated with slower improvement
	Asthma × time	+0.39	0.18	2.14	Asthma associated with slower improvement
	Total IgE × time	-0.26	0.06	-4.38	Higher IgE associated with faster improvement
TPS	Sex (male)	+0.70	0.32	2.18	Male sex associated with higher baseline TPS
	Allergy	-0.76	0.33	-2.33	Allergy associated with lower baseline TPS
	Total IgE	+0.70	0.10	6.86	Higher IgE associated with higher baseline TPS
	Total IgE × time	-0.02	0.01	-4.11	Higher IgE associated with faster polyp reduction
Sniffin' Sticks 16 Identity Score	Total IgE	-0.56	0.18	-3.07	Higher IgE associated with worse baseline smell
	AEC	-3.12	1.38	-2.26	Higher eosinophils associated with worse baseline smell
	Age × time	-0.03	0.01	-2.62	Older age associated with slower improvement
	Sex (male) × time	-0.05	0.02	-2.06	Male sex associated with slower improvement
	Total IgE × time	+0.03	0.01	2.66	Higher IgE associated with faster smell recovery

Baseline effects indicate associations with overall symptom or disease severity averaged across follow-up, while trajectory effects (interaction with time) indicate whether baseline factors modified the slope of change during treatment. Statistical significance was defined as $|t| \geq 2$ or <-2 ($p < 0.05$). AEC = Absolute Eosinophil Count, Ig = Immunoglobin, SNOT-22 = 22 item Sinonasal Outcome Test, TPS = Total Polyp Score.

follow-up, 62.7% of EPOS-eligible patients and 57.0% of EPOS-ineligible patients achieved adequate response, again with no significant difference (p=0.534).

Disease burden and N-ERD drive likelihood of adequate response

Multivariable logistic regression was performed to evaluate baseline predictors of EUFOREA-defined adequate response (Figure 1). N-ERD was the only independent predictor of response, associated with a significantly increased likelihood of achieving adequate response (OR 4.26, 95% CI 1.31–13.78; p=0.016). In contrast, higher baseline subjective and endoscopic disease burden was associated with a reduced likelihood of achieving adequate response. Higher total polyp score (TPS) (OR 0.78, 95% CI 0.61–0.99; p=0.039) and SNOT-22 (OR 0.69, 95% CI 0.52–0.91; p=0.009) independently predicted lower odds of achieving adequate response. Other baseline factors were not independently associated with treatment response (Table S2).

Longitudinal mixed-effects analyses suggest an association between baseline type 2 inflammatory burden and disease trajectories

Longitudinal mixed-effects modelling identified baseline serum total IgE as the most consistent predictor of both baseline disease severity and subsequent treatment response across key outcomes (Table 4). Higher IgE levels were associated with worse disease at initiation, including higher SNOT-22 scores (+5.03 ± 1.05, t=4.79), higher TPS (+0.70 ± 0.10, t=6.86), and poorer olfactory function (–0.56 ± 0.18, t=–3.07). Despite this greater baseline disease burden, elevated IgE was also associated with more favorable treatment trajectories, predicting faster improvement in SNOT-22 (interaction –0.26 ± 0.06, t=–4.38), TPS (–0.02 ± 0.01, t=–4.11), olfactory function (+0.03 ± 0.01, t=2.66). Other covariates demonstrated outcome-specific effects. Male sex and asthma were associated with slower improvement in SNOT-22, while older age and male sex were associated with slower recovery of olfactory function. Baseline differences were also observed, with male sex associated with higher TPS and better SNOT-22 scores, and allergy status associated with lower baseline TPS. Across secondary clinical outcomes (AQLQ and ACT), effects were more heterogeneous, with baseline IgE associated with worse asthma control and quality of life, but with mixed and outcome-specific influences on longitudinal change depending on sex, allergy status, and N-ERD. For inflammatory biomarkers, relationships were largely confined to biological coherence rather than clinical trajectories, with strong cross-associations between eosinophils and ECP, and differential effects of N-ERD, prior surgery, and baseline inflammatory burden on biomarker reduction over time. Full details of these interactions are provided in Table 3 and Table S3.

Discussion

In this study EPOS-eligible patients showed greater improvement in TPS, SNOT-22, and olfaction, with higher MCID attain-

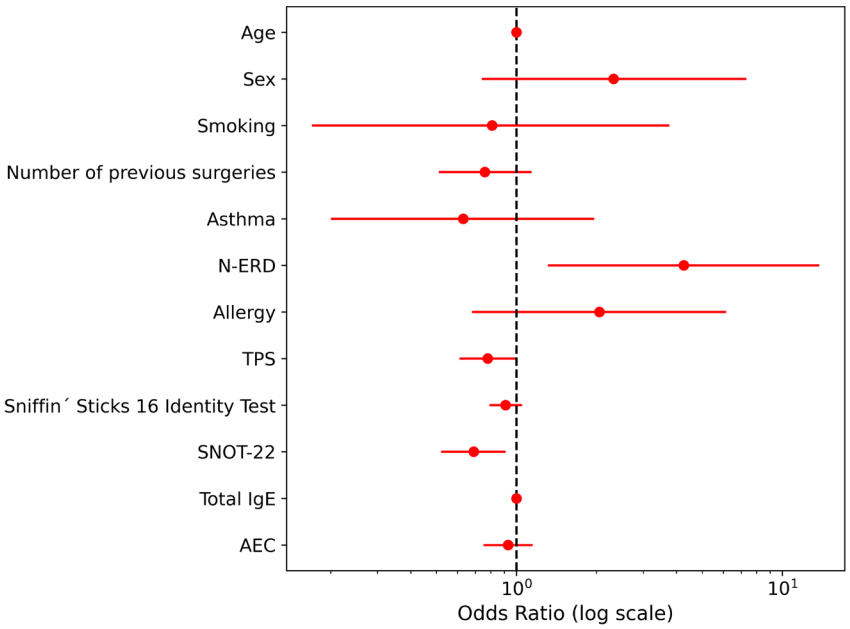

Figure 1. Forest plot of multivariable logistic regression results for baseline predictors of adequate response to dupilumab. Odds ratios (ORs) with 95% confidence intervals from multivariable logistic regression for baseline predictors of achieving adequate response to dupilumab according to EUFOREA criteria at the last available follow-up. Points represent odds ratios and horizontal lines represent 95% confidence intervals on a logarithmic scale. The vertical dashed line indicates an OR of 1. Odds ratios greater than 1 indicate an increased likelihood of achieving adequate response, whereas odds ratios less than 1 indicate a reduced likelihood. Numeric predictors were entered as linear terms, such that odds ratios represent the change in odds associated with a 1-unit increase in the predictor, except for SNOT-22, which was modelled per 10-point increase. Absolute eosinophil count (AEC) was modelled per 0.1 × 10^9/L increase and total IgE per 10 kU/L increase. Binary variables were modelled as presence versus absence of the characteristic (sex: male vs female).

ment and overall response scores. However, EUFOREA-defined "adequate response" did not differ between groups, suggesting limited applicability of threshold-based outcomes in EPOS ineligible patients. N-ERD independently predicted adequate response, while higher baseline IgE was associated with worse initial disease but faster improvement. Our results suggest that baseline disease severity and prominent evidence of Type 2 inflammation are important predictors of response to dupilumab. The effectiveness of EPOS 2020 in identifying CRSwNP patients who may benefit from dupilumab therapy is also confirmed by several real-world studies [17, 25-29]. Cohorts of EPOS 2020-eligible patients demonstrated significant disease control and restoration of quality of life within 12 months of treatment, with mean SNOT-22 scores decreasing by over 30 points, nasal polyp scores by more than 4 points, and olfactory function by over 5 points [25, 26]. Studies with longer follow-up also showed that such statistically significant improvements persisted at 24 months [28, 30] with a recent 5-year study of CRSwNP showing benefit at 36 months and beyond, with mean delta changes of -3.02 for polyp scores, -5.00 for SNOT-22, and +1.5 for smell function [17]. Our data, covering a follow-up period of up to 4.5 years, agree with these data and confirm the substantial benefits of dupilumab in EPOS-eligible patients, with the EPOS-eligible group exhibiting larger reductions in polyp burden, greater improvements in symptom scores and olfactory performance. Importantly EPOS-eligible patients had greater baseline disease burden by the nature of the indication criteria. This greater baseline severity increased the potential for larger absolute improvements and higher MCID attainment during dupilumab treatment. Therefore, the observed differences support the clinical utility of EPOS 2020 criteria for identifying patients with substantial modifiable disease burden. The superiority of screening patients using EPOS 2020 indication criteria before initiating dupilumab therapy is further supported by a real-world study, which included 71% EPOS 2020-eligible and 29% non-eligible CRSwNP patients. This cohort demonstrated greater improvements in both SNOT-22 and nasal polyp scores among EPOS-eligible patients [19]. In that cohort, failure to reach the SNOT-22 MCID was more common among patients not meeting EPOS 2020 indication criteria, supporting a less consistent treatment benefit in this group [19]. Similarly, EPOS-ineligible patients in our cohort more often failed to achieve the SNOT-22 MCID than EPOS-eligible patients (23.0% vs 10.7%), although meaningful symptom improvement can still occur in non-eligible patients, as also shown by CHRINOSOR [29].

In our cohort, EUFOREA-defined adequate response at 12 months was similar between EPOS-eligible and EPOS-ineligible

patients (68.0% vs 62.5%), despite greater improvements in TPS, SNOT-22, olfaction, and continuous EPOS/EUFOREA response scores among EPOS-eligible patients. This suggests that "adequate response" may better reflect low residual disease activity or remission-like control than the full magnitude of improvement from baseline, consistent with DUPIREAL, where 34.3% failed to meet the "4-outcome response" despite low symptom burden and high satisfaction in many patients [31].

Beyond EPOS eligibility, our analyses suggest that markers of type 2 inflammatory disease burden may further help identify patients most likely to benefit from dupilumab. N-ERD was the strongest independent predictor of EUFOREA-defined adequate response, consistent with the recognised type 2 inflammatory burden in this subgroup and real-world evidence supporting dupilumab efficacy in CRSwNP with N-ERD [16, 30, 32-34]. In longitudinal analyses, higher baseline IgE, another marker of type 2 inflammation, was associated with greater baseline disease burden and faster improvement in SNOT-22, TPS, and olfaction, although these effects were modest [35]. Previous studies have shown that dupilumab reduces IgE levels in CRSwNP, but the value of baseline IgE as a response predictor remains uncertain, with conflicting real-world data [36-39]. Taken together, our findings should not be interpreted as evidence that any single biomarker independently determines response due to the retrospective nature of this study, but rather as supporting a broader signal that type 2 inflammatory activity, assessed through both clinical phenotype and biomarkers, is central when evaluating suitability for dupilumab therapy.

Given the substantial cost of biologic therapy, appropriate patient selection is clinically and economically important. Dupilumab has been estimated to cost substantially more than ESS and first-line biologic strategies may markedly increase healthcare expenditure compared with surgery-first approaches [14, 40]. In contrast, ESS with maintenance topical corticosteroids provides durable disease control for many patients [41] and recent data is increasingly showing the value of complete prior surgery in disease control [42-44]. Our data support EPOS 2020 criteria as a useful framework for identifying patients most likely to benefit, while also suggesting that optimal candidates are those with persistent disease despite appropriate surgery and topical therapy, alongside clear evidence of type 2 inflammation [29].

This study provides robust real-world evidence on dupilumab outcomes in CRSwNP stratified by EPOS 2020 criteria. Strengths include a large cohort with extended follow-up, comprehensive assessment across clinical, patient-reported, and biomarker outcomes, and complementary analytical approaches enabling evaluation of both clinically relevant and independent predictors of response. Several limitations should be considered. The retrospective design introduces potential selection bias and incomplete data capture. Adjustment within EPOS group comparisons was not performed, as this would involve controlling for variables that define the groups themselves. The EPOS 2020 indication criteria represents a composite construct; therefore, baseline differences between groups are inherent, and EPOS-stratified analyses are not intended to isolate individual components, which were instead examined using multivariable and longitudinal modelling. The adapted EPOS/EUFOREA response assessment may introduce bias due to variable baseline applicability of domains. Multiple exploratory analyses increase the risk of type I error, and findings should be considered hypothesis-generating. Finally, the use of EMA-based prescribing criteria resulted in a broader, more heterogeneous cohort, potentially attenuating differences between EPOS groups. While this reflects real-world practice in Austria, generalisability may be limited in settings with stricter eligibility criteria.

Conclusion

EPOS 2020 indication criteria remain a robust framework for identifying patients who benefit most from dupilumab. Beyond these established guidelines, our data highlight additional predictors, particularly evidence of significant type 2 inflammatory burden, which may further refine patient selection.

Abbreviations

ACT: Asthma Control Test; CRS: Chronic Rhinosinusitis; CRSwNP: Chronic Rhinosinusitis with Nasal Polyps; ENT: Ear, Nose, Throat; EPOS: European Position Paper on Rhinosinusitis and Nasal Polyps; EUFOREA: European Forum for Research and Education in Allergy and Airway Diseases; IL: Interleukin; IQR: Interquartile Range; AQLQ: Asthma Quality of Life Questionnaire; MCID : Minimal Clinically Important Difference; N-ERD: NSAID Exacerbated Respiratory Disease; NSAID: Non-Steroidal Anti-Inflammatory Drugs; QoL: Quality of Life; SD: Standard Deviation; SNOT-22: 22 Item Sino Nasal Outcome Test; Th: T-Helper Cell; TPS: Total Polyp Score; VAS: Visual Analogue Score.

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None to declare.

Author contributions

SS and NJC had the initial idea for the retrospective analysis and SS, NJC, TJB, KG, AT, FF, and NM performed all data collection. NJC, SS, DP and JED interpreted the data and designed the figures. All authors wrote and critically revised the manuscript together. CM advised on key statistical analyses.

Conflict of interest

JED served as a speaker and/or consultant and/or advisory board member for Sanofi, AstraZeneca, and GSK. JED is an investigator for Sanofi, GSK and AstraZeneca (grants paid to her institution). SS served as a speaker and/or consultant and/or advisory board member for Sanofi and Novartis. SS is an investiga-

tor for Novartis and AstraZeneca (grants paid to his institution). The other authors declare no conflict of interest.

Ethic approval and consent to participate

Retrospective analysis of this patient population was approved by the Ethical Committee at the Medical University of Vienna (EK: 1340/2025).

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SUPPLEMENTARY MATERIAL

Table S1. Summary of Minimal Clinically Important Difference (MCID) definitions and their sourced literature.

Outcome	MCID Definition	Reference
TPS	≥ 1-point decrease	Bachert C, Khan AH, Hopkins C, Blaiss MS, Soler ZM, Nash S, et al. Rapid and Continuing Improvements in Nasal Symptoms with Dupilumab in Patients with Severe CRSwNP. J Asthma Allergy. 2022;15:557-63.
SNOT-22	≥ 8.9-point decrease	Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. Clin Otolaryngol. 2009;34(5):447-54.
Sniffin' Sticks 16 Identity Score	≥ 1-point increase	Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G. 'Sniffin' sticks': olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. Chem Senses. 1997;22(1):39-52.
ACT	≥ 3-point increase	Schatz M, Kosinski M, Yarlas AS, Hanlon J, Watson ME, Jhingran P. The minimally important difference of the Asthma Control Test. J Allergy Clin Immunol. 2009;124(4):719-23 e1.
AQLQ	≥ 0.5-point increase	Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. J Clin Epidemiol. 1994;47(1):81-7.
Allergy VAS	≥ 1-point change	Bousquet PJ, Combescure C, Klossek JM, Daures JP, Bousquet J. Change in visual analog scale score in a pragmatic randomized cluster trial of allergic rhinitis. J Allergy Clin Immunol. 2009;123(6):1349-54.

ACT = Asthma Control Test, AQLQ = Asthma Quality of Life Questionnaire, EPOS = European Position Paper on Rhinosinusitis and Nasal Polyps, SNOT-22 = 22 item Sinonasal Outcome Test, TPS = Total Polyp Score, VAS = Visual Analogue Scale.

Table S2. Multivariable logistic regression of baseline predictors for adequate response to dupilumab at the last available visit.

Variable	OR	95% CI (Lower)	95% CI (Upper)	p-value
Age	1.00	0.97	1.04	0.859
Sex (male)	2.32	0.74	7.32	0.151
Smoking	0.81	0.17	3.76	0.783
Number of previous ESS surgeries	0.76	0.51	1.14	0.189
Asthma	0.63	0.20	1.96	0.422
N-ERD	4.26	1.31	13.78	0.016
Allergy	2.05	0.68	6.15	0.201
TPS	0.78	0.61	0.99	0.039
Sniffin' Sticks	0.91	0.79	1.05	0.192
SNOT-22	0.69	0.52	0.91	0.009
Total IgE	1.00	0.99	1.01	0.692
AEC	0.93	0.75	1.15	0.499

Table showing adjusted odds ratios (ORs) with 95% confidence intervals from multivariable logistic regression for baseline predictors of achieving "adequate response" to dupilumab according to EUFOREA criteria at the last available follow-up. Odds ratios greater than 1 indicate an increased likelihood of achieving adequate response, whereas odds ratios less than 1 indicate a reduced likelihood. Predictors measured on numeric scales were entered as linear terms, such that odds ratios represent the change in odds associated with a 1-unit increase in the predictor: age per year, TPS per 1-point increase, Sniffin' Sticks 16 Identity Test score per 1-point increase, SNOT-22 per 10-point increase, number of previous surgeries per additional surgery, total IgE per 10 kU/L increase, and absolute eosinophil count per 0.1×10^9/L increase. Binary predictors were modelled as presence versus absence of the characteristic. AEC = Absolute Eosinophil Count, ESS = Endoscopic Sinus Surery, Ig = Immunoglobulin, N-ERD = non-steroidal anti-inflammatory drug (NSAID) Exacerbated Respiratory Disease, SNOT-22 = 22 item Sinonasal Outcome Test, TPS = Total Polyp Score.

Table S3. Baseline predictors of dupilumab treatment trajectory in disease related outcomes identified using linear mixed-effects models.

Outcome	Predictor	Estimate	Std Error	t value	Interpretation
AQLQ	Sex (male)	+8.76	2.76	3.17	Male sex associated with better baseline QoL
	Allergy	-6.10	2.89	-2.12	Allergy associated with worse QoL
	Total IgE	-2.80	0.86	-3.25	Higher IgE associated with worse QoL
	Sex (male) × time	-0.34	0.10	-3.34	Male sex associated with faster improvement
	N-ERD × time	-0.23	0.11	-2.12	AERD associated with faster improvement
	Allergy × time	+0.21	0.10	2.22	Allergy associated with slower improvement
	Total IgE × time	+0.14	0.05	3.02	Higher IgE associated with slower improvement
ACT	Total IgE	-0.42	0.21	-2.00	Higher IgE associated with worse asthma control
	Sex (male) × time	-0.07	0.03	-2.65	Male sex associated with faster improvement
AEC	ECP	+0.15	0.02	10.1	Higher ECP associated with higher eosinophils
	N-ERD × time	+0.01	0.01	3.52	N-ERD associated with slower reduction
	Number of previous surgeries × time	-0.01	0.01	-2.57	More surgery associated with faster reduction
	ECP × time	+0.01	0.01	4.63	Higher ECP associated with slower reduction
ECP	AEC	+2.64	0.17	15.2	Higher eosinophils associated with higher ECP
	N-ERD × time	-0.01	0.01	-2.62	N-ERD associated with faster reduction
	AEC × time	-0.03	0.01	-5.99	Higher eosinophils associated with faster reduction
IgE	Sex (male)	+0.60	0.20	2.96	Male sex associated with higher IgE
	Asthma	+0.49	0.23	2.15	Asthma associated with higher IgE
	Allergy	+0.46	0.21	2.21	Allergy associated with higher IgE

Baseline effects indicate associations with overall symptom or disease severity averaged across follow-up, while trajectory effects (interaction with time) indicate whether baseline factors modified the slope of change during treatment. Statistical significance was defined as $|t| \geq 2$ or <-2 ($p < 0.05$). ACT = Asthma Control Test, AEC = Absolute Eosinophil Count, AQLQ = Asthma Quality of Life Questionnaire, ECP = Eosinophilic Cationic Protein, Ig = Immunoglobin, NERD = NSAID Exacerbated Respiratory Disease.