

Effect of Dupilumab on Radiological Remission in Patients with Chronic Rhinosinusitis with Nasal Polyp: A One Step Forward Toward Clinical Remission

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Background and Objectives: While achieving complete radiological improvement in patients with nasal polyps is often observed following surgical resection, the impact of biologic therapy, specifically dupilumab, on polyp size is an area of great interest. The objective of this study was to assess the effect of dupilumab in patients with chronic rhinosinusitis with nasal polyps (CRSwNP) by assessing nasal polyps using the computed tomography (CT) staging system, Lund–Mackay score (LMS).

Methods: A two-year prospective cohort study was conducted on 29 patients diagnosed with CRSwNP and asthma and eligible for dupilumab as an add-on therapy. The study involved comprehensive assessments of patients before biologic initiation and after the study. These assessments included clinical, laboratory, and radiological evaluations.

Results: Dupilumab treatment reduces LMS across sinuses ($p < 0.001$) and improves nasal obstruction ($p = 0.001$). Blood eosinophil count (BEC) predicts persistent sinus obstruction, doubling the likelihood per unit increase (odds ratio: 1.67, $p = 0.02$). BEC levels identify persistent nasal obstruction (AUC: 76%, $p = 0.04$), with a cutoff point above 255.5 cells per microliter, revealing a sensitivity of 100% and a specificity of 42%. The probability of persistent nasal obstruction at the 20th month is 55%, regardless of prior nasal polyp surgery ($p = 0.41$).

Conclusion: Dupilumab led to significant radiological improvements in patients with CRSwNP, demonstrating a potential role of radiological remission, irrespective of prior nasal polyp surgery. Additionally, BEC levels may guide the likelihood of persistent nasal obstruction.

Keywords: chronic rhinosinusitis with nasal polyps, dupilumab, radiological remission, Lund–Mackay score

Introduction

Chronic rhinosinusitis (CRS) is a common condition that affects 5–28% of the general population worldwide.¹ It significantly burdens healthcare utilization and productivity loss.² In adults, CRS is characterized by inflammation of the nose and paranasal sinuses, with two or more symptoms lasting at least three months.³ These symptoms include nasal blockage, discharge, facial pain, and reduction or loss of smell.⁴ Endoscopic or Computed Tomography (CT) scan evidence of abnormalities such as nasal polyps, mucosal changes, or sinus involvement is also necessary.⁵ The prevalence of CRS is narrowed down to 3–6% when verified by endoscopy and/or CT scan.¹ CRS is traditionally categorized into two types: chronic rhinosinusitis with nasal polyps (CRSwNP) and without nasal polyps (CRSsNP). CRSwNP is characterized by bilateral, endoscopically visualized polyps in the middle meatus, while CRSsNP lacks

visible polyps in the middle meatus, confirmed if necessary following decongestant uses.⁶ The CRSwNP phenotype affects approximately 1–2.5% of the population.¹ Many factors might affect the course of CRSwNP, such as age of onset, smoking habits, allergy, asthma, and disease severity.⁷ Asthma coexists in 30–70% of CRSwNP patients.⁸ However, 10–30% of patients with mild asthma and 70–90% of severe asthma patients suffered from nasal polyps.⁹

Despite optimal medical treatment and repeated surgeries, a significant number of CRSwNP patients remain uncontrolled, underscoring the imperative for innovative therapeutic approaches.¹⁰ Initially approved for severe asthma, biologic therapies now emerge as a promising solution for patients with CRSwNP and delivering personalized care.^{7,11,12} This therapy employs monoclonal antibodies targeting the type-2 inflammatory pathway by inhibiting agents such as IL-4 receptor (IL-4R), IL-5, and IgE.^{13,14}

Dupilumab, a fully human monoclonal antibody, effectively inhibits the signaling of IL-4 and IL-13 by binding to the alpha subunit of IL-4R types 1 and 2.^{15,16} Dupilumab is the first FDA-approved biologic for treating CRSwNP in adults.¹⁷ Administered as an add-on therapy alongside intra-nasal corticosteroids (INCS), dupilumab has garnered positive opinions from the European Medicine Agency (EMA) and the Italian Medicines Agency.^{18,19} In Italy, it is recommended as an adjunctive therapy with INCS for adult patients grappling with severe, uncontrolled CRSwNP.¹⁸

Remission, marked by the absence of symptoms and objective disease markers, is becoming a key goal in managing chronic conditions.²⁰ While well-established in Rheumatology and Gastroenterology, the concept is now emerging in respiratory medicine for asthma.^{20–22} It is crucial to understand that remission is not the same as cure or disease modification. The latter requires the patient to return to a normal physiological state with no signs or symptoms of the disease and no need for ongoing treatment. Remission may indicate temporary improvement, but it does not necessarily mean the disease has been eliminated. The Global Initiative for Asthma (GINA) has recently identified remission as a treatment objective. The consensus panel has differentiated between clinical remission and complete remission. Clinical remission is a significant improvement of symptoms with stable lung function, agreement between the patient and provider on remission, and no systemic corticosteroid use for at least 12 months. However, complete remission includes the objective resolution of asthma-related inflammation and, if applicable, a negative bronchial hyper-responsiveness test. Remission off treatment means no asthma treatment for at least 12 months.^{23,24} The question will be whether disease remission could also be applied to CRSwNP. While achieving complete radiological remission of nasal polyps is often observed following surgical resection, the impact of biologic therapy, specifically dupilumab, on polyp size is an area of great interest. The primary objective of this study was to assess the effect of dupilumab in patients with CRSwNP by assessing nasal polyps using the computed tomography (CT) staging system, known as the Lund-Mackay score (LMS). The secondary objectives were evaluating the clinical aspect of patients while focusing on the quality of life, olfactory evaluation, and associated asthma symptoms.

Methods

Study Design and Patients' Inclusion and Exclusion Criteria

A prospective cohort study was conducted at Al-Rashed Allergy Center in Kuwait from May 2021 to April 2023. Patients above 18 years with CRSwNP associated with asthma were included. Asthma diagnosis was based on symptom variability and reversibility of forced expiratory volume in one second (FEV1%); inconclusive initial spirometry results led to further tests like peak expiratory flow (PEF) variability and fractional exhaled nitric oxide (FeNO) for confirmation.²⁵ However, CRSwNP diagnosis relied on clinical criteria, with all patients who had undergone functional endoscopic sinus surgery (FESS) assessed using endoscopic assessment for nasal polyps and a CT scan for sinuses indicating polypoidal nasal mucosal thickness based on EPOS 2020 guidelines.²⁶ Additionally, individuals with moderate-to-severe CRSwNP were assessed for eligibility for dupilumab therapy (600 mg as an initial dose administered subcutaneously, followed by a maintenance dose of 300 mg every two weeks according to the same guidelines.²⁶ Moreover, all recruited patients were on appropriate medical therapy, including the use of regular topical steroid nasal

sprays or rinses, as per EPOS 2020 guidelines.²⁶ Compliance with this treatment regimen was closely monitored through patient self-reports and regular follow-up visits to ensure adherence.

Those undergoing dupilumab treatment for a minimum of three months were included. Exclusions comprised individuals below 18 years, those with CRSwNP only (without asthma), patients who had undergone sinus surgery within the last 12 months, and those declining to participate or complete the study.

Ethics Approval and Consent to Participate

All participants had provided written informed consent, indicating their complete understanding of the nature and objectives of the research. Participation was voluntary, and they willingly agreed to participate after being fully informed. The study approved from Kuwait University and the Ministry of Health ethical committee office with approval number (2121/2022), which was aligned with local guideline as well the Helsinki Declaration protocol. This protocol ensured that the research was conducted ethically and adhered to globally recognized standards.

Sample Size

The sample size was calculated using Minitab 17.1.0.0 for Windows software (Minitab Inc., 2013, Pennsylvania, USA) with considerations for a type I error of 0.05 and a type II error of 0.2. Referring to two prior study,^{27,28} where the median difference in LMS was 4 and IQR about 4 before and after dupilumab therapy,²⁷ and mean SNOT-22 changes were 42 with a standard deviation of 22, the minimum paired sample size needed was determined to be 15 to ensure a study power exceeding 80%.

Data Collection and Outcome

Demographic information, such as age and sex, along with disease-related data, including the number of nasal polyp surgeries and the frequency of oral corticosteroid (OCS) courses in the year preceding the initiation of dupilumab, was systematically gathered from patients' records.

The evaluation of patient outcomes involved a comparative analysis of the following parameters at two distinct time points: baseline (prior to the commencement of dupilumab treatment) and at the end of the study:

1. Olfactory symptoms

The determination of hyposmia or anosmia was conducted through one-on-one interviews, with or without using a Visual Analogue Scale (VAS) questionnaire.²⁹

2. Quality of life assessment

We used the verified Italian version of the Sino-nasal outcome test (SNOT-22), which provides scores ranging from 0 to 110. SNOT-22 score of less than 20 indicated mild symptoms.³⁰ During subsequent evaluations, we regarded an 8.9-point growth in SNOT-22 scores as the minimum clinically significant difference, as recorded in previous research.³¹

3. Frequency of exacerbations requiring a short cycle of OCS course; 20mg of prednisolone for 5 days.

4. Asthma symptoms

The ACT score was used to assess the effectiveness of asthma treatment. It assesses the severity of shortness of breath, overall asthma symptoms, use of rescue medications, impact on daily activities, and self-rated asthma control. Using a 5-point scale range from 1 (always) to 5 (never) for symptoms and activities and 1 (not controlled) to 5 (completely controlled) for overall control. The scores range between 5 (poor control) to 25 (complete control), with higher scores indicating better asthma control. The ACT score above 19 suggested that the patient's asthma is well-controlled.³²

5. Spirometry

Post bronchodilator parameters, including FEV1% predicted, FVC% predicted, and FEV1/FVC% predicted, were collected.

6. Type 2 inflammatory markers

The FeNO level was measured from the participant's exhaled breath. However, the blood samples were collected to measure BEC, we ensured that BEC measurements were taken during periods when participants were either stable on their OCS regimen or had a consistent dosage over a specified period to reduce the impact of short-term fluctuations of BEC.

7. Radiological assessment

All patients underwent CT scans for paranasal sinuses (PNS), which were carried out using a 64-multislice scanner with a slice thickness of 0.6–1.0 mm at 120 Kv and 80–160 mAs. In addition, sagittal and coronal reconstructions were also included. An experienced Radiologist interpreted the results using the LMS.³³ Each sinus – maxillary, anterior ethmoid, posterior ethmoid, sphenoid, and frontal – received a score ranging from 0 to 2, which indicated the severity of opacification. The ostiomeatal complexes (OMC) region was scored 0 or 2, which meant not occluded or occluded. The scores ranged from 0 to 24, and our proposed categories were 0–10 for normal or mild obstruction (Figure 1A), 11–23 for partial obstruction (Figure 1B), and 24 for complete obstruction (Figure 1C), and we considered changes from complete and partial obstruction to normal or mild obstruction as a radiological remission as shown in Figure 2.

Statistical Analysis

The data were collected in an Excel sheet, and statistical analysis was conducted using Minitab for Windows (version 17.1.0.0, Minitab Inc, Pennsylvania, USA). For numerical data, mean and standard deviation or median and inter-quartile range were used, while categorical data were presented as numbers and percentages. To compare differences before and after treatment, paired t-tests or Mann–Whitney tests were employed, along with the chi-square test. Logistic regression analysis was applied to find the predictors of blood eosinophil count for persistent nasal obstruction. Additionally, Receiver Operating Characteristic (ROC) curves were utilized to determine the discrimination utility of blood eosinophils, identifying the optimal cutoff point with higher sensitivity and specificity. Significance was considered for an area under the curve above 0.6. Pearson correlation coefficients were calculated to estimate the linear relationship between LMS, SNOT-22, and other numerical factors. The sign before “r” indicated the direction of the relationship. A trend analysis with a quadratic model was employed to fit changes in LMS over the duration of dupilumab treatment and identify the best regression curve. For survival analysis of persistent nasal obstruction within a 24-month follow-up of dupilumab treatment in patients with or without prior nasal polyp surgery, Kaplan-Meier with Log rank tests was used. All tests were two-sided, and significance was set at $p < 0.05$.

Results

About 29 patients with CRSwNP and asthma recruited in the study, all of them received dupilumab for at least 3 months in the duration from May 2021 to April 2023. The mean (SD) age of CRSwNP patients was 48 (13) years and the majority were male (68.97%). Over two-thirds of these patients had undergone polypectomy before initiating dupilumab as a treatment option, with a median (range) number of surgeries at about 2 (1–12) (Supplementary Table 1).

Table 1 summarizes the clinical characteristics of patients before and after the initiation of dupilumab. Notably, there were significant improvements in the severity of SNOT-22, symptoms of anosmia and hyposmia, the need for OCS, ACT, FEV1% and FVC% predicted ($p < 0.05$ for all).

Furthermore, Table 2 demonstrates a significant decrease in the LMS within each individual group of PNS as well as in the overall total LMS ($p < 0.05$ for all). Moreover, out of the 6 patients experiencing total nasal obstruction (20.96%),

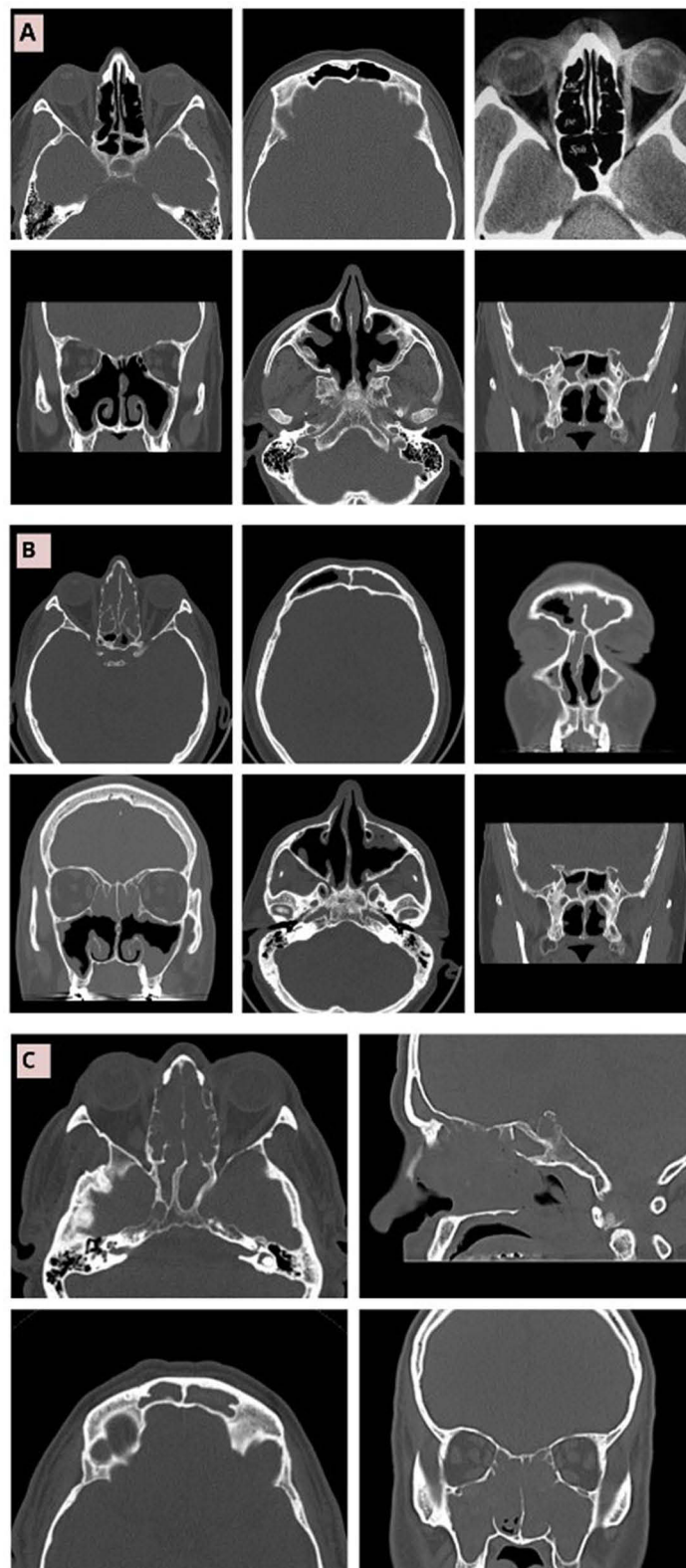


Figure 1 CT for groups of PNS. **(A)** PNS with normal and mild obstruction: The figure showed mild opacification of both maxillary and both sphenoid sinuses with clear frontal, anterior ethmoid, posterior ethmoid with non-obstructed ostiomeatal complexes, with a score of less than 10 of 24 according to LMS. **(B)** PNS with partial obstruction: In this figure there were partial opacification of Rt. frontal, total opacification of Lt. frontal, sinuses, total opacification of both anterior ethmoid, partial opacification of both posterior ethmoid, partial opacification of both maxillary sinuses, partial opacification of both sphenoid with non-obstructed both ostiomeatal complexes, with a score of (11–23) of 24 according to LMS. **(C)** PNS with total obstruction: The figure showed total bilateral opacification of frontal, anterior ethmoid, posterior ethmoid, sphenoid and ostiomeatal complexes; with a score of 24/24 according to LMS.

LMS from 0-10 for normal or mild obstruction
 LMS from 11-23 for partial obstruction
 LMS of 24 for complete obstruction

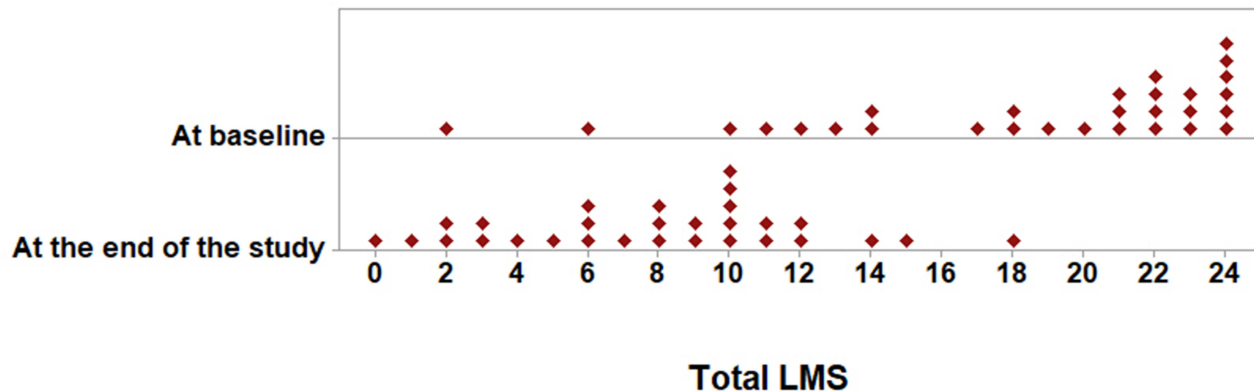


Figure 2 Dot plot of LMS at base line and at the end of the study.

there was a tendency for complete remission following treatment with a significant p-value of 0.001. Additionally, among the 20 patients (68.97%) initially presenting with moderate sinus obstruction, the number decreased to 7 (24.14%). Remarkably, there was a significant rise in the number of patients with mild obstruction, increasing from 3 (10.34%) before treatment to 22 (75.86%) after treatment, with a p-value less than 0.001. So far, after treatment, 24.14% of patients exhibited persistent sinus obstruction, characterized by moderate obstruction with an LMS ranging from 11 to 23.

The patients received biological treatment for 3 months as minimum, the median period was 12 month and IQR ranged from 8 to 17 months ([Supplementary Table 1](#)). [Figure 3](#) unveils a quadratic trend model and represented the relationship between dupilumab treatment duration and LMS. This model hinted at a potential curvilinear connection, suggesting a more complex pattern of impact over time. Specifically, it reveals a plausible acceleration phase in the action of dupilumab, showcasing a notable reduction in LMS until the 9th month of treatment. This is succeeded by a plateau phase, observed up to the 15th month, and eventually a deceleration phase extending to the 24th month. Despite the accuracy demonstrated by this quadratic model, the presence of a nuanced pattern involving acceleration and deceleration implied the influence of additional factors on the radiological remission. The complexity of the observed trend suggests that while dupilumab played a significant role in reducing LMS, there may be other contributing factors that influence the radiological outcomes.

Table 1 Clinical Follow Up of Patients

Factors	Before (n=29)		After (n=29)		p
SNOT-22, mean, SD	65.75	20.88	26.62	20.54	<0.001 [†]
OCS (Yes), n, %	18	62.07	1	3.45	<0.001*
Anosmia/hyposmia (Yes), n, %	28	96.55	5	17.24	<0.001*
Poor-AC (Yes), n, %	12	41.38	3	10.34	<0.001*
ACT, median, IQR	20	(14.75–22)	22.5	(20–24.25)	<0.001 ^{††}
FeNO (ppb), median, IQR	23	(16–40)	14	(12–23)	<0.001 ^{††}
BEC (cells/microL), median, IQR	430	(240–645)	350	(210–575)	0.63
FEV1% predicted, mean, SD	80.39	11.35	87.04	14.52	0.02 [†]
FVC % predicted, median, IQR	82.36	9.49	88.64	10.63	<0.001 ^{††}
FEV1/FVC % predicted, mean, SD	83.76	8.99	87.67	10.70	0.07

Notes: [†]Paired t-test, ^{††}Mann Whitney test, *Chi square test, p<0.05 considered significant, the bold numbers represent significant correlation.

Abbreviations, N, number; SNOT-22, Sino-nasal Outcome Test-22; OCS, Oral corticosteroid; AC, asthma control; ACT, asthma control test; FeNO, fractional exhaled nitric oxide; BEC, Blood eosinophil count; FEV1, Forced expiratory flow in 1 second; FVC, Forced vital capacity.

Table 2 Radiological Follow Up of Patients Using LMS

Factors	Before (n=29)			After (n=29)			P
Frontal sinus, Q1, median, Q3	2	4	4	0	1	2	<0.001 ^{††}
Anterior ethmoidal sinus, Q1, median, Q3	3.5	4	4	1.5	2	2	<0.001 ^{††}
Posterior ethmoidal sinus, Q1, median, Q3	2	4	4	0	2	2	<0.001 ^{††}
Maxillary sinus, Q1, median, Q3	2	3	4	2	2	2	<0.001 ^{††}
Sphenoid sinus, Q1, median, Q3	2	3	4	0	1	2	<0.001 ^{††}
Ostiomeatal complex, Q1, median, Q3	2	4	4	0	0	0	<0.001 ^{††}
Total LMS, Q1, median, Q3	14	21	23	4	8	10	<0.001 ^{††}
Complete obstruction, n, %	6	20.69		0	0		0.001*
Moderate obstruction, n, %	20	68.97		7	24.14		<0.001*
Mild obstruction, n, %	3	10.34		22	75.86		<0.001*

Notes: ^{††}Mann Whitney test, *Chi square test, p<0.05 considered significant, the bold numbers represent significant correlation.

Abbreviations: Q1: Quartile 1, Q3: Quartile 3, n: number.

The factors predicting persistent sinus obstruction, after adjusting for age and sex, are detailed in Table 3. It is illustrated that for every one-unit increase in BEC, the likelihood of total sinus obstruction doubled, with an odds ratio of 1.67 and a p-value of 0.02.

The effectiveness of blood eosinophils in identifying persistent nasal obstruction was prominent, showing good utility. This was evident in Figure 4, where the area under the curve (AUC) was 76%, with a p-value of 0.04. The sensitivity and specificity were calculated at a cutoff point of >255.5 cells per microliter, revealing a sensitivity of 100% and a specificity of 42% (Table 4).

The survival probability for persistent nasal obstruction reached 55% at the 20th month of treatment with dupilumab in patients who had undergone nasal polyp surgery previously (Figure 5); this percentage was not significantly different from those who had not undergone surgery (p=0.41).

The correlation between the severities of PNS obstruction, measured using LMS, and sinonasal manifestations in SNOT-22 demonstrated no significant correlation, neither before nor after the initiation of dupilumab (detailed in Supplementary Table 2). Moreover, before the use of dupilumab, LMS exhibited a significant negative correlation

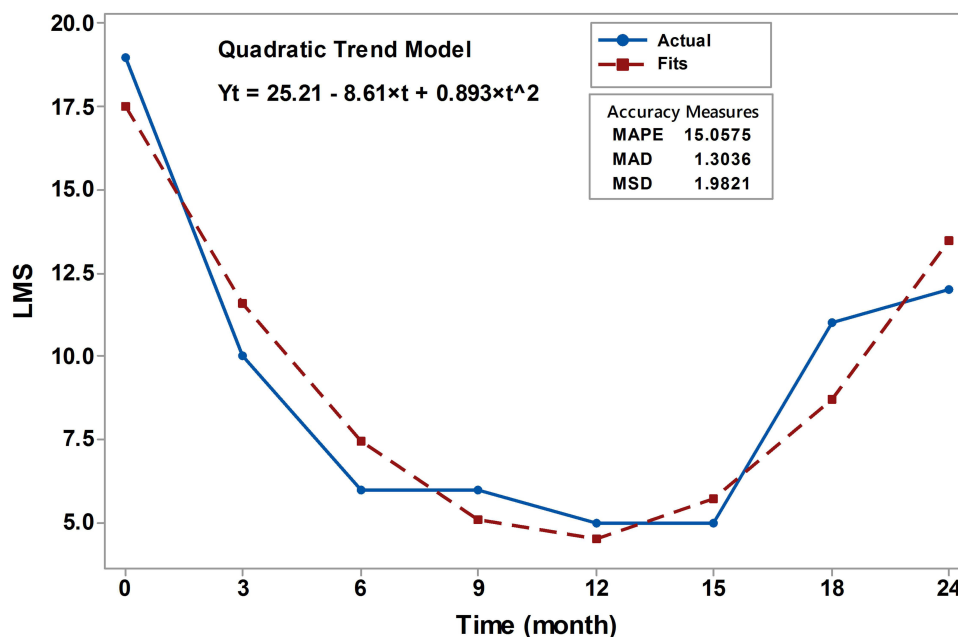


Figure 3 Trend plot of LMS within the time of dupilumab treatment.

Table 3 Predictors of Persistent Sinus Obstruction

Factors	OR	95% CI	P
Treatment duration (month)	0.96	(0.8014, 1.1637)	0.71
Age (Year)	1.02	(0.9457, 1.1163)	0.51
BEC (cells/microL)	1.68	(1.0000, 1.9857)	0.04
Male-sex	0.67	(0.0382, 8.8476)	0.99

Notes: The test of fitness: Hosmer-Lemeshow, Chi-Square=8.9, P-value=0.37, the test of significant: logistic regression model with adjustment for age and sex, $p < 0.05$ considered significant, the bold numbers represent significant correlation.

Abbreviations: BEC, blood eosinophil count; OR, odd ratio; CI, confidence interval.

with FeNo levels but did not correlate significantly with BEC. After the administration of dupilumab, the correlation with BEC became significantly positive, with no correlation with FeNo level. However, SNOT-22 demonstrated a significant negative correlation with ACT both before and after dupilumab usage, without any significant correlation with FEV1, FeNO, or BEC (Figure 6).

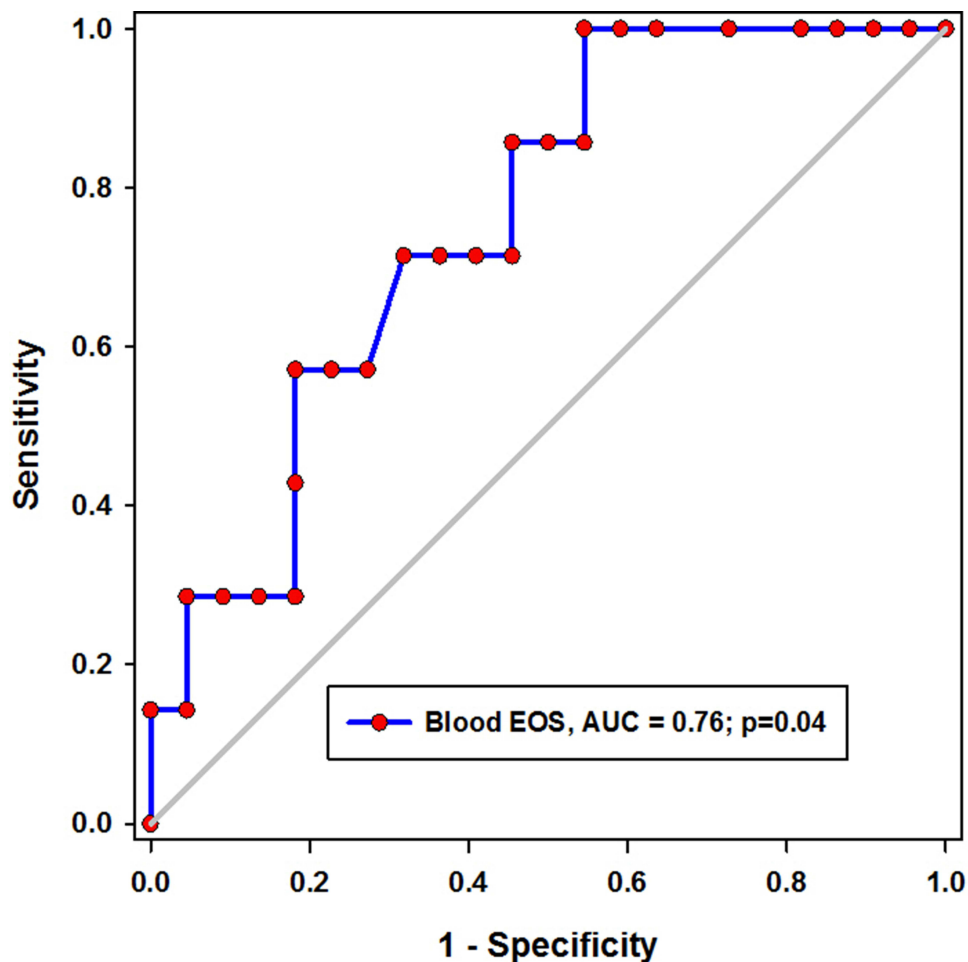


Figure 4 ROC curve of blood eosinophil in identifying persistent nasal obstruction.

Abbreviations: AUC, area under curve; EOS, eosinophil.

Table 4 Utility of Blood EOS in Detecting Persistent Nasal Obstruction

Cutoff >	Sensitivity	95% CI	Specificity	95% CI	PPV	NPV
255 (cells/microL)	100%	0.4782 to 1.000	45%	0.2211 to 0.6336	29%	100%

Abbreviations: CI, Confidence interval; PPV, positive predictive value; NPV, negative predictive value.

Discussion

Disease remission has become a target outcome for many chronic inflammatory diseases, driven by the revolutionary development of new biological therapies. This trend, initially established in Rheumatology and Gastroenterology²⁰ and extended to asthma,^{21,22} is guided by the 2020 expert consensus panel. According to this panel, clinical remission of asthma can be considered when the following features persist for at least 12 months: no use of systemic steroids, optimization or stabilization of current lung function, absence of significant asthma symptoms using a validated tool such as the ACT score, and mutual agreement between the patient and provider about remission.^{23,24}

The present study focused on 29 patients with a confirmed diagnosis of CRSwNP and associated asthma. Dupilumab influenced the clinical features of associated asthma toward clinical remission, resulting in improved asthma control and reduced OCS usage. However, radiological evaluation of PNS revealed a notable trend towards radiological remission; a significant revolutionary shift towards a normal state or mild inflammation in nasal obstruction was observed.

In rheumatoid arthritis (RA), a reduction in finger joint space width (JSW) is associated with joint damage. A recent study³⁴ compared changes in JSW from baseline to week 52 in RA patients treated with Certolizumab pegol (CZP) in

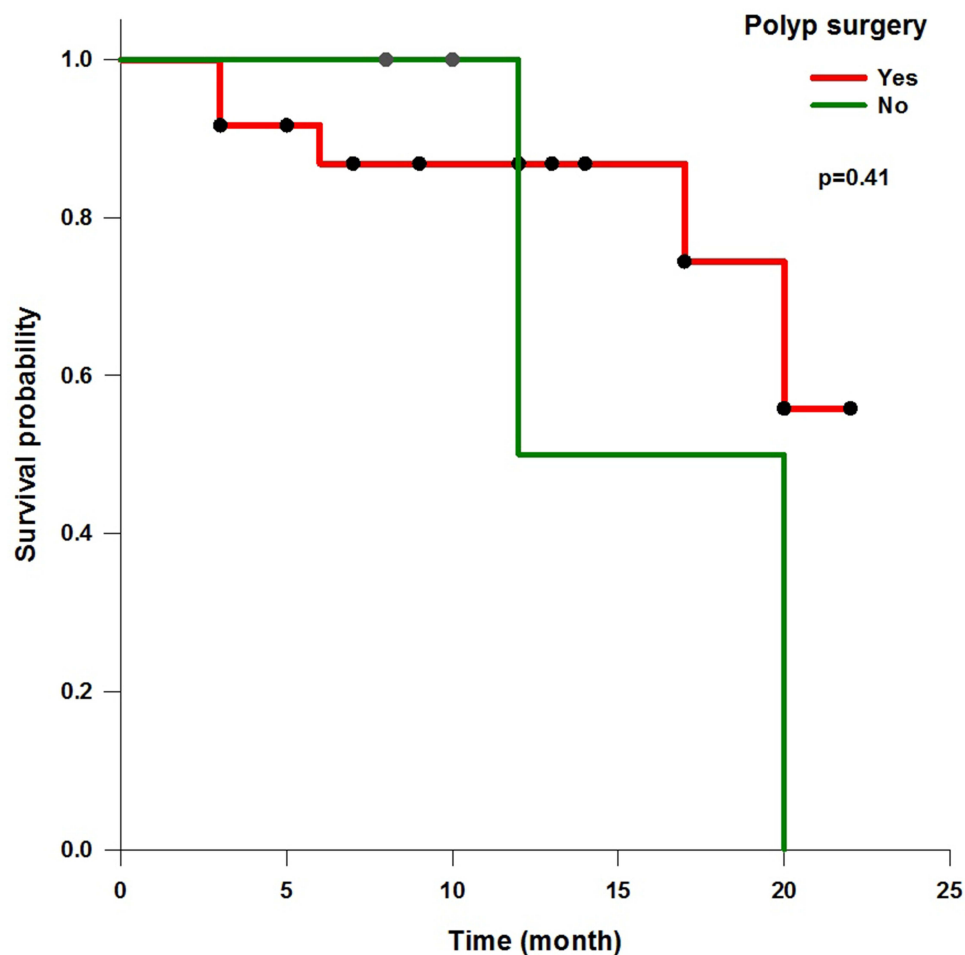


Figure 5 Survival probability of persistent nasal obstruction after dupilumab treatment.

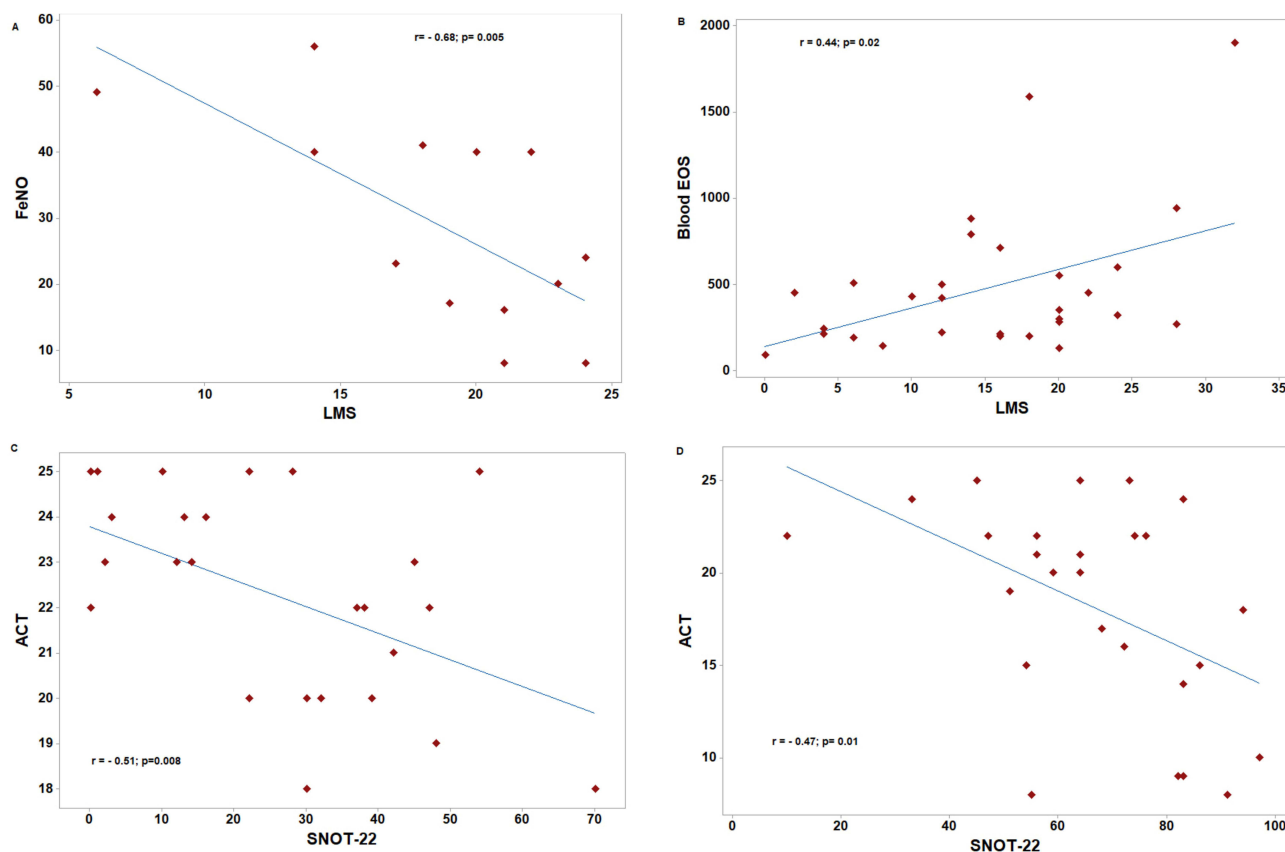


Figure 6 Correlation between LMS and SNOT-22 with other clinical parameters before and after dupilumab. The test of significant: Pearson correlation coefficient, $p < 0.05$ considered significant, the sign before “r” denotes the direction of relationship, (A) Correlation between LMS and FeNo before dupilumab, (B) Correlation between LMS and BEC after dupilumab, (C) Correlation between SNOT-22 and ACT before dupilumab, (D) Correlation between SNOT-22 and ACT after dupilumab.

combination with methotrexate (MTX) versus those treated with MTX/placebo. The findings revealed a significant clinical remission in patients receiving CZP plus MTX, accompanied by increased joint space, and this finding suggests a potential radiographic remission in rheumatoid arthritis; so far, the radiological remission term could be used as an objective tool for evaluating the clinical remission of patients with CRSwNP too, as we hypothesized in the current study. Moreover, some literature suggests incorporating radiological remission, assessed through modern tools like ultrasonography (US) and magnetic resonance imaging (MRI), into the criteria for evaluating RA remission. These modern tools are crucial as these advanced imaging techniques often reveal sub-clinical inflammation in patients considered clinically in remission, emphasizing the persistent risk of joint damage and potential disease activity flare.³⁵

In addition to the radiological remission, we observed favorable responses to dupilumab treatment, evident in both clinical outcomes and specific inflammatory markers. Significant improvements were noted in olfactory symptoms and quality of life (SNOT-22), and all symptomatic and functional parameters related to associated asthma showed enhancement. The need for OCS courses diminished to nearly zero. However, concerning type 2 inflammatory markers, only FeNO significantly decreased during treatment, while BEC did not reach a statistically significant reduction post-treatment. Moreover, the type 2 inflammatory markers did not correlate with the patient’s quality of life, measured by SNOT-22, either before or after dupilumab. In a supportive Japanese study, 49 patients with CRSwNP were followed for up to 52 weeks. The primary endpoints at week 24 were assessed, including nasal polyp score (NPS), nasal congestion (NC) score, and LMS. Of the 45 patients who completed the study, significant improvements in NPS, NC score, and LMS were observed at week 24 with dupilumab compared to the placebo. The study suggested that dupilumab rapidly and significantly enhanced clinical outcomes for CRSwNP in Japan, maintaining consistent safety and efficacy across the study population.³⁶

Furthermore, in dupilumab-treated patients either in SINUS-24 and SINUS-52 analysis, the results suggested a connection between the efficacy of dupilumab, as assessed by a reduction in nasal polyp score (NPS), and a decrease in certain local biomarkers associated with nasal type 2 inflammation in severe CRSwNP. While the aforementioned study did not reveal strong correlations with systemic measurements, it highlights the need for further exploration into the specific biomarkers that best align with objective measures of disease severity and patient-reported outcomes.³⁷ In essence, robust and consistent correlations between biomarker changes and clinical improvements in CRSwNP remain un-established; however, it could be related to the complexity of CRSwNP pathophysiology, and even though it did not interfere with the potential localized impact of dupilumab on type 2 inflammation in the nasal cavity.

In the present study, prior to initiating dupilumab treatment, we observed that elevated LMS were linked to reduced levels of FeNO. However, this association was not statistically significant with BEC. Following the commencement of dupilumab, a novel positive correlation emerged between LMS and BEC. These findings underscore the transformative impact of dupilumab on the interplay between radiological profiles and markers of type 2 inflammation, suggesting a potential shift in the inflammatory dynamics among patients with CRSwNP undergoing dupilumab treatment.

To date, no study has explored the correlation among the three aspects of CRSwNP remission, encompassing clinical, laboratory, and radiological remission. Despite the limited size of our cohort, this study carries substantial weight in suggesting the potential convergence of these terms. It provides a compelling indication of how the disease may stabilize and progress towards a comprehensive remission phase. Another noteworthy aspect of this study is the timing of the observed successful effects of dupilumab. It showcased a notable reduction in LMS scores until the 9th month of treatment, followed by a continuous plateau phase observed up to the 15th month. Despite the accuracy of the quadratic model trend, the nuanced pattern involving acceleration and deceleration implies the influence of additional factors on radiological remission. The complexity of the observed trend suggests that while dupilumab played a significant role in reducing LMS, other contributing factors may influence radiological outcomes. As mentioned previously, 7 out of 29 patients (24.1%) continued to experience persistent partial obstruction in PNS-CT. Notably, the level of BEC independently predicted this persistent partial obstruction state, with the likelihood doubling with every unit increase in blood eosinophils. The sensitivity of blood eosinophils above 255 cells per microliter was 100%, effectively discriminating between the presence and absence of subclinical inflammation.

CRSwNP involves eosinophilic tissue infiltration and type 2 inflammation, where IL-5 activates and sustains eosinophils.³⁸ Though their exact contributions to CRSwNP pathology remain uncertain, eosinophilia/IL-5 elevation is a possible biomarker for higher recurrence rates of nasal polyps post-surgery.^{39–41} Our findings suggest that eosinophils are independent predictors of persistent nasal obstruction post-treatment. Combining BEC with concomitant asthma can gauge the risk of NP recurrence post-surgery.⁴² Less invasive methods, such as BEC and nasal secretions, are promising for quantifying eosinophilia in CRSwNP.³⁸ The current results highlight the potential clinical relevance of this biomarker in predicting treatment outcomes.

Although biologics have revolutionized the treatment of nasal polyposis, their cost, potential side effects, and superiority over surgery in treating CRSwNP are concerning.⁴³ While some studies have examined the use of biologics in a broader population, surgical options that provide comparable outcomes at a lower cost are still being debated.^{44,45} Biologics should be part of CRSwNP management, but surgical and standard therapies are also practical and cost less.⁴³ In our study, after 20 months of dupilumab treatment, the survival rate for patients with persistent nasal obstruction was 55%, regardless of whether they had undergone nasal polyp surgery. This result suggested that dupilumab could be a viable alternative to surgery for patients with this condition, which has a high rate of recurrence. Long-term biological therapy could be a promising solution to this issue.

Limitation

A crucial limitation was the small sample size, which impacts the broader applicability of the current findings. Additionally, the use of only two biomarkers related to type 2 inflammation may limit the comprehensive assessment of dupilumab's impact on a broader array of inflammatory markers. Another notable limitation is the absence of a control group, which restricts our ability to make more robust comparisons and fully assess the efficacy of dupilumab in contrast to standard therapies or placebo. Furthermore, the variability in treatment duration among patients introduces

heterogeneity into the results, as some were on therapy for the entire study period while others had a shorter duration. The lack of systematic screening for aspirin-exacerbated respiratory disease (AERD), a known factor influencing disease severity, may also affect the generalizability of the findings. Additionally, olfactory function was assessed through one-on-one interviews and a Visual Analogue Scale (VAS) questionnaire, which may not be as accurate as specialized testing for smell function. Our center was not equipped to perform more precise olfactory tests, which are typically conducted at ENT specialized centers. Finally, while patients were instructed to use regular topical steroids, adherence was self-reported, potentially introducing bias as actual compliance might differ from reported use.

Conclusion

This study introduced the term “radiological remission” as an objective measure reflecting clinical remission in patients with CRSwNP treated with dupilumab. Additionally, the response to dupilumab demonstrated acceleration toward the stabilization phase within the initial 15 months of treatment, prompting consideration of the potential for persistent nasal obstruction or recurrence of inflammation. Notably, the estimation of BEC emerged as an independent predictor for discerning the likelihood of these outcomes.

Data Sharing Statement

The datasets used during the current study available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

All participants had provided written informed consent, indicating their complete understanding of the nature and objectives of the research. Participation was voluntary, and they willingly agreed to participate after being fully informed. The study approved from Kuwait University and the Ministry of Health ethical committee office with approval number (2121/2022), which was aligned with local guideline as well the Helsinki Declaration protocol. This protocol ensured that the research was conducted ethically and adhered to globally recognized standards.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, took part in drafting, revising the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare no conflict of interest. Each author has revised and approved the final version of the manuscript independently.

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