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Comparison of Modified Lund–Kennedy Endoscopic Score and Nasal Polyp Score in the Follow-Up of Patients with Severe Uncontrolled CRSwNP During Biological Therapy

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Abstract: Chronic rhinosinusitis with nasal polyps (CRSwNP) is a persistent inflammatory disorder of the upper airways, severely impacting quality of life. Dupilumab, targeting type 2 inflammatory pathways, is effective in managing severe, uncontrolled CRSwNP. However, the comparative accuracy of endoscopic scoring systems in monitoring therapeutic response to dupilumab remains unclear. This study compared the accuracy of the nasal polyp score (NPS) and the modified Lund–Kennedy endoscopic score (M-LKS) in assessing dupilumab response. Methods: A retrospective cohort analysis included 66 severe CRSwNP patients treated with dupilumab at Padua University. Endoscopic scores (NPS and M-LKS), patient-reported outcome mesures (PROMs), and clinician-reported outcome measures (CROMs), including peak nasal inspiratory flow (PNIF) and the Sniffin' Sticks test, were evaluated at baseline and over 24 months. Results: Both NPS and M-LKS showed significant reductions over time ($p < 0.001$), significantly correlating with PNIF ($p < 0.001$). Given time and patient, PNIF emerged to be the only covariate related to endoscopic scores. No significant differences were observed between NPS and M-LKS regarding clinical outcome associations, suggesting equivalent accuracy. PNIF was identified as a critical predictor of endoscopic improvement, highlighting its clinical utility. These findings reinforce the role of standardized endoscopic metrics in assessing the efficacy of biologic therapies for CRSwNP.

Keywords: CRSwNP; Lund–Kennedy score; nasal polyp score; NPS; nasal endoscopy; dupilumab

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1. Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a persistent inflammatory disorder of the upper airways, characterized by a diffuse involvement of both nasal fossae and the paranasal sinuses. It accounts for 25–30% of all chronic rhinosinusitis (CRS) cases and it considerably impairs patients' quality of life (QoL) [1]. CRSwNP is a multifactorial disease associated with genetic factors, immune system abnormalities, anatomical variations. The disease process is further complicated by its interaction with external environmental factors, such as airborne pollutants and allergens, but also microbial agents such as viruses, bacteria, and fungi. These intrinsic factors highlight the complexity of its pathophysiology. In this regard, CRSwNP is predominantly driven by a type 2 inflammatory response, a pattern

that is especially prevalent in Western populations, characterized by elevated levels of interleukin (IL)-4, IL-5, and IL-13, elevated tissutal eosinophils, macrophages, type 2 innate lymphoid cells, and mast cells [2–5]. Furthermore, it has been observed that CRSwNP is frequently associated with type 2 driven comorbid condition, such as asthma, allergies to inhalants, and non-steroidal anti-inflammatory drugs (NSAIDs) intolerance, presenting with a greater impact on patients' quality of life and a poorer response to conventional treatments [6].

At present, endoscopic examination remains a cornerstone in CRSwNP evaluation, both for diagnostic and follow-up purposes, allowing for the assessment of the disease burden and its response to medical and surgical treatment through a direct visualization of the nasal mucosa and its associated inflammatory changes. Key endoscopic features include mucus characteristics, such as viscosity and color, as well as nasal polyps (NP) volume and distribution, both considered as indicative of the underlying inflammatory endotype and disease severity [7]. In this regard, several scores have been proposed to standardize endoscopic finding, with the "nasal polyp score (NPS)" [8] and the "modified Lund–Kennedy endoscopic score (M-LKS)" (Figure 1) being two of the most largely adopted all over the globe [9]. These scores are validated for clinical and research use and have been proved to be reliable in detecting rhinological conditions changes over time, including the effects of both medical and surgical intervention [10].

A

NPS	Description
0	No nasal polyps.
1	Small nasal polyps in the middle meatus not reaching below the inferior border of the middle turbinate.
2	Nasal polyps reaching below the lower border of the middle turbinate.
3	Large nasal polyps reaching the lower border of the inferior turbinate or nasal polyps medial to the middle turbinate.
4	Large nasal polyps causing complete obstruction of the inferior nasal cavity.

B

	M-LKS	Description
Polyps	0	None
	1	In middle meatus only
	2	Beyond middle meatus
Oedema	0	Absent
	1	Mild
	2	Severe
Discharge	0	None
	1	Clear and thin
	2	Thick and purulent

Figure 1. (**A**) nasal polyp score (NPS) description; (**B**) modified Lund–Kennedy endoscopic score (M-LKS) description.

Over the past years, the management of severe uncontrolled CRSwNP has undergone a notable shift with the introduction of humanized monoclonal antibodies targeting specifically type 2 inflammation pathway. In particular, several real-life setting studies published in the literature have demonstrated the remarkable effectiveness of dupilumab in CRSwNP management [3,11]. It has been largely established that biologic drugs substantially improve both clinician- and patient-reported outcome measures (CROMs and PROMs, respectively) with benefits becoming evident as early as week four of treatment [12]. Despite the significant effectiveness of biologic therapies, a considerable variability in the degree of response to such therapies is observed, which are currently classified into three categories (poor, moderate and excellent response) according to EUFOREA 2023 criteria [13]. In this regard, the reduction in polyp size, mostly evaluated by means of NPS, despite being one of the main criteria identified in the EUFOREA 2023 guidelines [13], does not consider other relevant endoscopic features of CRSwNP such as mucosal edema or nasal discharges.

The aim of the present study is therefore to compare M-LKS and NPS accuracy in evaluating CRSwNP response to dupilumab therapy.

2. Materials and Methods

2.1. Population

The present investigation consists of a retrospective study in a real-life setting involving the rhinological unit of Padua University. The study was conducted in accordance with the 1996 Helsinki Declaration and was approved by each Hospital ethical committee (5304/AO/22). Informed consent on personal data collection and use for research purposes was obtained from each subject before starting the treatment, as routinely done in our Rhinological Unit for every patient initiating dupilumab for CRSwNP. Inclusion criteria were defined as follows: (1) age $\geq$ 18 years; (2) diagnosis of severe chronic rhinosinusitis with nasal polyps (CRSwNP), defined by a nasal polyp score (NPS) $\geq$ 5 and/or a Sinonasal Outcome Tests-22 (SNOT-22) $\geq$ 50 with inadequate symptoms control despite the use of intranasal corticosteroids (INCS), receiving at least two cycles of systemic corticosteroid in the previous 12 months and/or having undergone one or more endoscopic sinus surgery (ESS) (according to The Italian Medicine Agency cut-off for dupilumab reimbursement); (3) biological therapy administration (dupilumab 300 mg, one subcutaneous injection every 15 days) for at least 6 months; (4) NPS and M-LKS collection at each timepoint.

Severe uncontrolled CRSwNP was diagnosed in accordance with the criteria of the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020 [3]. All patients included in the study were regularly using intra-nasal corticosteroids (INCS) before and throughout the whole study period. The INCS active principles included were either mometasone furoate 50 µg 2 sprays in each nostril once or twice a day or budesonide 100 µg 1 spray in each nostril once a day. Asthmatic patients regularly used a combination of long-acting beta agonist (LABA) and inhaled corticosteroids (ICS) and never discontinued the treatment.

Data were collected at the following timepoints: baseline (before the biological treatment was begun) (T0), 1 month (T1), 3 months (T2), 6 months (T3), 12 months (T4), 18 (T5), and 24 months (T6) after starting the treatment.

Demographic data, clinical and surgical history, inhalants allergy, smoking habit, and the number of oral corticosteroids (OCS) short courses in the previous 12 months were collected at T0. At baseline and at each follow-up, the following PROMs were collected to estimate patients' QoL and symptoms burden: SNOT-22 questionnaire [14], visual analogue scale (VAS) for nasal obstruction (VAS-NO), smell impairment (VAS-Smell), facial pain (VAS-facial pain), and sleep disturbance (VAS-sleep) [15]. Furthermore, the following CROMs were collected: peak nasal inspiratory flow (PNIF) meter (Clement Clark International, Mountain Ash, UK), to evaluate nasal patency [16]; Sniffin' Sticks identification sub-test (SSIT) (12 odors) (Burghart Messtechnik GmbH, Holm) [17], to categorize the smell impairment into anosmia, hyposmia and normosmia.

All the patients underwent nasal endoscopy using a 0○ and or 30○ rigid endoscope, during which NPS and M-LKS were collected. The first focuses on NP size and distribution, evaluating each nasal fossa separately and scoring from 0 (no polyps) to 4 (large polyps causing complete obstruction of the inferior meatus), thus providing a total score ranging from 0 to 8 [8]. The second one investigates three items on each side, consisting of NP size and distribution, mucosal edema severity, and nasal discharge characteristics, with a score ranging from 0 to 2 to each item, thus providing a total score ranging from 0 to 12 (Figure 1). Blood eosinophilia was evaluated at baseline and at each timepoint [9].

2.2. Statistical Analysis

Quantitative variables were presented as median and interquartile range [IQR], whereas categorical variables were expressed as number of observations and percentage (%). The paired Wilcoxon test was also used to compare quantities between timepoints.

The Bravais–Pearson correlation coefficient was used to measure the relations between the different indicators.

Multiple mixed linear longitudinal regression with a selection of variables based on Akaike's information criterion (hybrid backward stepwise) were executed to identify the effects of the available variables on the measurement changes in time.

For all tests, p-values were calculated; 5% was considered as the critical level of significance, while values within the range of $0.10 > p \leq 0.05$ were considered as the statistical trend. All the analyses were performed in R (R Core Team, 2021) [18].

3. Results

A cohort of 66 patients (54 males and 12 females, median age 58 [47.3–64.8] years) undergoing dupilumab treatment as add-on therapy were included in the present study. Patients' demographics and both PROMS and CROMS at baseline (T0) are reported in Table 1. In total, 52 patients reached the 12-month follow-up, while 29 patients reached the 2-year follow-up threshold.

Table 1. Patients' main clinical characteristics at baseline: PROMs, patient's reported outcome measures; CROMs, clinician's reported outcome measures; yr, years; IQR, interquartile range; BMI, body mass index; N-ERD, non-steroidal anti-inflammatory drugs exacerbated respiratory disease; OCS, oral corticosteroids; ESS, endoscopic sinus surgery; VAS, visual analogue scale; -NO, nasal obstruction; SNOT-22, Sinonasal Outcome Test-22; SSIT, Sniffin' Sticks identification test; NPS, nasal polyp score; LKS, Lund–Kennedy endoscopic score; *: OCS short course per year.

Demographics	**Sex**	**Median Age, yr [IQR]**	**BMI, Median [IQR]**	**Asthma, n (%)**	**N-ERD, n (%)**	**Allergy to Inhalants, n (%)**	**Smokers, n (%)**	**OCS *, Median [IQR]**	**ESS, Median [IQR**
	54 M (82%) 12 F (18%)	58 (47–65)	25.3 (23.2–27.8)	41 (62.1%)	17 (25.8%)	33 (50%)	7 (10.6%)	2 (1.7–2.2)	1 (1–2)
PROMs and CROMs	**VAS-NO, median [IQR]**	**VAS-smell, median [IQR]**	**VAS-facial pain, median [IQR]**	**VAS-sleep, median [IQR]**	**SNOT-22, median [IQR]**	**PNIF, median [IQR]**	**SSIT, median [IQR]**	**NPS, median [IQR]**	**LKS, median [IQR]**
	7.5 (6–9)	10 (9–10)	5 (2–8)	6 (2.5–7.5]	56 (39.2–68)	120 (75–157.5)	3 (3–6)	6 (5–6)	6 (4–8)

A significant decrease in both NPS and M-LKS was observed ($p < 0.001$) throughout the study period (Figure 2). No statistically significant differences were observed when comparing the two endoscopic scores decrease ($p = 0.2$). A similar trend was observed for all the considered PROMs (SNOT-22, VAS-NO, VAS-Smell, VAS-Rhinorrhea, VAS-facial pain, and ACT), with a significant reduction throughout the study period ($p < 0.001$) (Figure 3). Additionally, all the other relevant CROMs (such as SSIT and PNIF) improved during the treatment ($p < 0.001$) (Figure 3).

We further considered the correlations between each endoscopic score (NPS and M-LKS) and the main PROMs and CROMs affected in CRSwNP patients [19]. In particular, no statistically significant correlation was found between SNOT-22 and both NPS and M-LKS. When considering the CROMs (SSIT and PNIF), a significant negative correlation was observed between PNIF and both M-LKS ($r = -0.005$, $p = 0.009$) and NPS ($r = -0.006$, $p < 0.001$). Similarly, SSIT negatively correlated with NPS ($r = -0.8$, $p = 0.04$) and showed a statistical trend with M-LKS ($r = -0.997$, $p = 0.06$), without differences between the two endoscopic scores ($p > 0.05$) (Table 2).

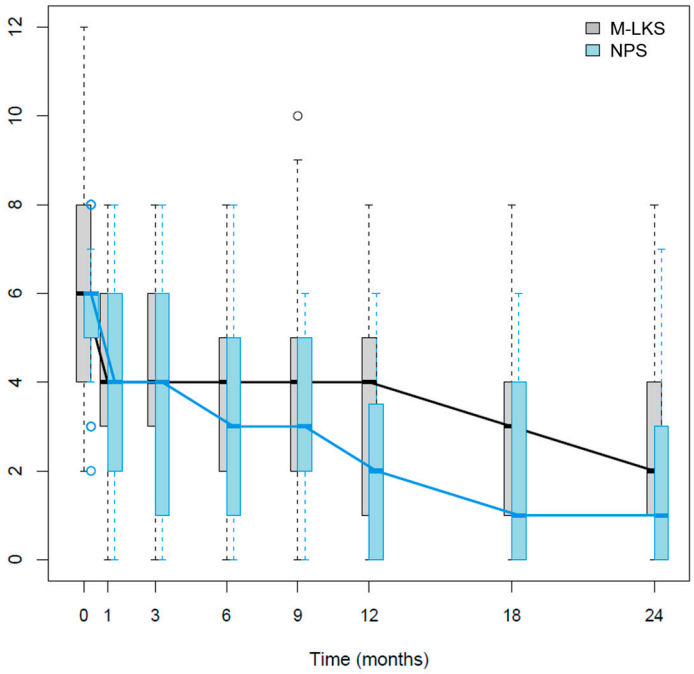

Figure 2. NPS and M-LKS changes during the study period. NPS, nasal polyp score; M-LKS, modified Lund–Kennedy endoscopic score.

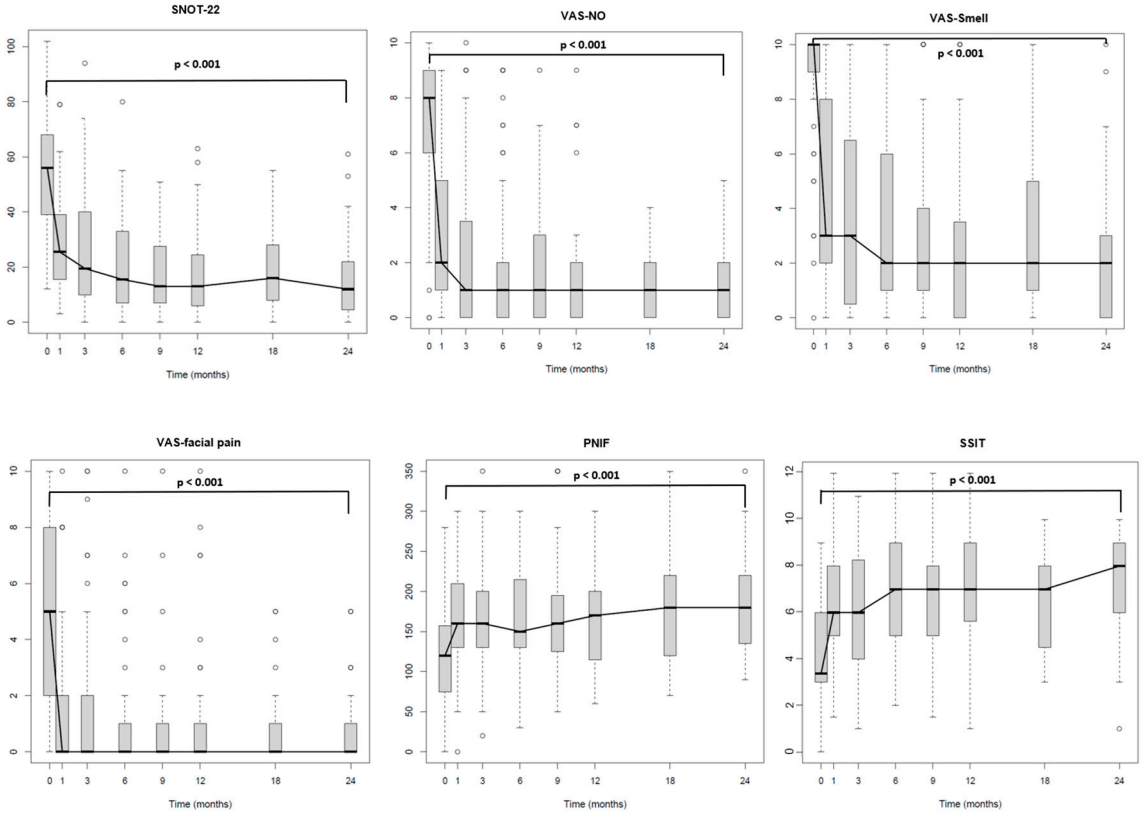

Figure 3. Patient-reported outcome measures (PROMs) and clinician-reported outcome measures (CROMs) changes during the study period. SNOT-22, Sinonasal Outcome Test-22; VAS, visual analog scale; NO, nasal obstruction; PNIF, peak nasal inspiratory flow; SSIT, Sniffin' Sticks identification test.

Table 2. Correlation between M-LKS, NPS, and the main PROMs and CROMs investigated. M-LKS, modified Lund–Kennedy endoscopic score; NPS, nasal polyp score; PROMs, patient-reported outcome measures; CROMs, clinician-reported outcome measures; SNOT-22, Sinonasal Outcome Test-22; VAS, visual analog scale; NO, nasal obstruction; PNIF, peak nasal inspiratory flow; SSIT: Sniffin' Sticks identification test.

	M-LKS		NPS	
	Correlation	*p Value*	*Correlation*	*p Value*
SNOT-22	0.002	0.773	0.003	0.587
VAS-NO	0.036	0.399	0.067	**0.038**
VAS-smell	0.042	0.249	0.100	**<0.001**
VAS-facial pain	−0.019	0.692	−0.035	0.331
VAS-sleep	0.016	0.719	0.023	0.500
SSIT	−0.997	0.06	−0.833	**0.041**
PNIF	−0.005	**0.009**	−0.006	**<0.001**
ACT	−0.035	0.171	−0.009	0.640

In the multivariate analyses, given time and patient, the only covariate showing a significant effect on both endoscopic scores was PNIF ($p < 0.001$ for both endoscopic scores) (Tables 3 and 4).

Table 3. Multivariate analyses to identify the effects of the variables on NPS changes during the follow-up. NPS, nasal polyp score; T, timepoint of visits; PNIF, peak nasal inspiratory flow.

	Estimate	Std. Error	df	t Value	Pr (>|t|)
(Intercept)	6.316710	0.314369	223.349543	20.093	***p* < 0.001**
T1	−0.804958	0.249023	400.737638	−3.232	***p* = 0.001**
T2	−1.556601	0.225303	399.689226	−6.909	***p* < 0.001**
T3	−2.019193	0.229423	400.105491	−8.801	***p* < 0.001**
T4	−2.151421	0.232079	400.476848	−9.270	***p* < 0.001**
T5	−2.474594	0.237109	401.021467	−10.437	***p* < 0.001**
T6	−3.014599	0.238966	398.860924	−12.615	***p* < 0.001**
PNIF	−0.005714	0.001532	455.698477	−3.731	***p* < 0.001**

Table 4. Multivariate analyses to identify the effects of the variables on M-LKS changes during the follow-up. M-LKS, modified Lund–Kennedy endoscopic score; T, timepoint of visits; PNIF, peak nasal inspiratory flow.

	Estimate	Std. Error	df	t Value	Pr (>|t|)
(Intercept)	6.782008	0.370056	273.111323	18.327	***p* < 0.001**
T1	−1.129586	0.386729	351.734044	−2.921	***p* = 0.003**
T2	−1.629318	0.319488	346.085347	−5.100	***p* < 0.001**
T3	−1.743885	0.329099	347.207783	−5.299	***p* < 0.001**
T4	−2.150819	0.321590	349.366157	−6.688	***p* < 0.001**
T5	−2.190922	0.326068	351.438568	−6.719	***p* < 0.001**
T6	−2.468237	0.328056	348.364357	−7.524	***p* = 0.009**
PNIF	−0.005115	0.001955	345.166486	−2.616	***p* < 0.001**

4. Discussion

This study compares two widely adopted endoscopic scoring systems for assessing patients with CRSwNP [9,20], specifically evaluating their changes following the administration of dupilumab as an add-on therapy for severe CRSwNP. The results demonstrated a significant and sustained decrease in both NPS and M-LKS over the study period, without differences between the two, confirming what was previously observed in a study conducted with [21], and highlighting their value as key objective measures for monitoring disease improvement during treatment. This response underscores the powerful anti-type 2 inflammatory effects of dupilumab on nasal mucosal swelling, nasal secretions, and polyp burden, which are pivotal to the pathophysiology of CRSwNP. Remarkably, the absence of a statistically significant divergence between the two endoscopic scores suggests that these scales are equally effective in capturing the endoscopic response to treatment, further validating their reliability for assessing disease progression and treatment response in this patient population. A similar pattern of improvement was also observed in all the other considered measurements, included in both PROMs and CROMs. This reflects dupilumab's outstanding efficacy across multiple domains of disease burden, underscoring its ability to significantly alleviate both symptoms and disease severity throughout the study period.

Notably, when looking at correlations, no statistically significant correlation was found between SNOT-22 and both endoscopic scores. Despite being one of the few validated PROMs for CRS, the discrepancy between SNOT-22 and the evaluated endoscopic scores is consistent to what has already emerged from previous studies in the literature [22]. This divergence contributes to demonstrate once again the absence of statistically significant correlation between the majority of PROMs and CROMs in functional sinonasal diseases. This aspect might be justified by the fact that PROMs, evaluating symptoms burden, are prone to be strongly influenced by patient subjectivity. On the other hand, significant correlations were observed between the endoscopic scores and the CROMs used to assess nasal patency and olfactory function. Specifically, PNIF demonstrated a significant negative correlation with both M-LKS and NPS. Similarly, SSIT negatively correlated with NPS and M-LKS. These findings suggest that the NP shrinkage, assessed by both endoscopic scores, surely has a significant positive effect on both patients' nasal patency and olfactory function. However, the evaluation of NP volume clearly appears to have a distinct influence on the two endoscopic scores, specifically being the only factor considered by NPS, while representing just one of different features evaluated by M-LKS. Notably, there were no significant differences in the respective NPS and M-LKS correlations with PNIF and SSIT. This can be explained by the fact that in the M-LKS, either the NP size reduction is impactful enough to significantly reduce the global system score, or the simultaneous mucosal edema and secretions reduction may synergically contribute to improve both PNIF and SSIT, leading to a decrease in the overall score comparable to the NPS reduction. On the other hand, considering that NP consists of only one of the predominant manifestations of nasal inflammation, the sole assessment of their reduction over time might be sufficient to monitor the decrease in the inflammatory burden in the majority of CRSwNP patients undergoing treatment with dupilumab. This is especially valuable in non-research setting patient evaluation, where the use of different and potentially redundant scores might unnecessarily and excessively prolong the duration of patients' assessment. Focusing on the correlation between both endoscopic score and the olfactory impairment, the olfactory recovery can likely be the result of an increased ventilation of the olfactory cleft followed by NP shrinkage, allowing a higher concentration of odorants to reach the olfactory epithelium [23]. Interestingly, on the one hand, these correlations contrast with what has already emerged from other studies in the literature, where olfactory recovery was independent of NP reduction [24]. On the other hand, these findings reflect the complex and multifactorial pathogenesis of

olfactory loss in type 2 CRSwNP, determined by both a "conductive" and a "sensorineural" impairment [24].

In the multivariate analysis, PNIF emerged as the only covariate that exhibited a significant effect on both NPS and M-LKS scores (Tables 3 and 4). This suggests that both the NP volume and the reduction in other nasal inflammatory manifestations (edema and secretions) due to dupilumab therapy allows an increase in nasal airflow measured by PNIF [19]. This finding positions PNIF as a valuable adjunctive marker for objectively tracking therapeutic efficacy.

While many studies on dupilumab have deeply investigated the relationships between NPS and other PROMs and CROMs [11,19,25], only a small number of real-life studies have evaluated M-LKS trends during dupilumab, with only a few focusing specifically on the comparison between M-LKS and NPS during biological or surgical therapy [26–32]. Although the M-LKS already considers the NP volume and studying both NPS and M-LKS scores together might not really change the course of diagnosis and outcome in these patients, monitoring changes in mucosal edema and discharge may reflect subtle mucosal improvements that are not captured by NPS alone, especially when potentially irreversible structural changes have developed in the nasal tissue [33]. This distinction might not have an immediate impact on clinical decision-making in the management of patients on biologics. However, it could contribute to a more comprehensive understanding of mucosal response and may help to refine endoscopic monitoring tools or composite outcome measures in the future. Additionally, the combined use of these measures may be particularly useful in distinguishing nuanced therapeutic responses in complex cases. This is especially relevant when evaluating the response to biologic therapy in a research setting, where the use of the two scoring systems may contribute to precisely assessing the inflammatory status of the disease. Consequently, the complementary use of both endoscopic scores would be paramount to better define disease control, disease remission, and, possibly, disease cure.

Limitations

The present study shows some limitations. Firstly, this is a monocentric study, involving only the rhinology unit of Padova University. Moreover, the retrospective design and relatively small sample size may limit the generalizability of the findings.

5. Conclusions

NPS and M-LKS appeared as reliable and complementary measures for assessing disease severity and treatment response in patients with CRSwNP undergoing dupilumab therapy. Both scores showed significant and sustained reductions, closely correlating with improvements in functional outcomes such as PNIF and SSIT. NP shrinkage plays a central role in improving olfactory function, likely due to increased olfactory cleft airflow but also to the reduced inflammation of the olfactory cleft mucosa. The correlation between M-LKS, NPS, PROMs, SSIT, and PNIF highlights the importance of a multimodal approach to evaluate CRSwNP response during biologic therapy. While NPS excels in monitoring rapid changes in polyp size, M-LKS captures broader inflammation-related disease features, providing a more comprehensive overview. The lack of significant differences between these two scores indicates that improvements in one parameter closely align with changes in the other. Future studies are solicited to further delineate their complementary roles to refine CRSwNP management strategies.

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G.O., T.S., S.Z. and N.T.; writing—review and editing, G.R., G.O. and T.S.; visualization, G.R., G.O., T.S., S.Z., N.T., A.F. and P.N.; supervision, G.O. and P.N.; project administration, G.R. and G.O. All authors have read and agreed to the published version of the manuscript.

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Abbreviations

The following abbreviations are used in this manuscript:

CRSwNP	Chronic rhinosinusitis with nasal polyps
NPS	Nasal polyps score
M-LKS	Modified Lund–Kennedy endoscopic score
PROMs	Patient-reported outcomes
CROMs	Clinician-reported outcomes
PNIF	Peak nasal inspiratory flow
CRS	Chronic rhinosinusitis
QoL	Quality of life
INCS	Intra-nasal corticosteroids
OCSVAS	Oral corticosteroidsVisual analog scale
VAS-NO	Visual analog scale for nasal obstruction
SSIT	Sniffin' Sticks test
NP	Nasal polyps

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