

Correlation of polyp grading scales with patient symptom scores and olfaction in chronic rhinosinusitis: a systematic review and meta-analysis*

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Abstract

Background: Various nasal polyp (NP) scoring systems have been proposed and used in the literature. However, no single system has been identified as superior. Correlations between NP scoring systems and patient symptoms, quality of life (QOL) or olfaction vary widely.

Methods: A systematic search of PubMed, CINAHL, Scopus, and Cochrane Library was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses guideline. Any study examining endoscopy scores and symptom, QOL or olfaction measures in cross sectional manner or after therapeutic intervention were included.

Results: This review identified 55 studies for a pooled meta-analysis of Lund-Kennedy (LK-NP) polyp scores (N = 6), Meltzer scores (N = 6), Nasal polyp scores (NPS; N = 19), Total polyp score (TPS; N=8) Lilholdt scores (N = 8), Olfactory cleft endoscopy score (OCES; N=4), Discharge, inflammation, polyp/edema score (DIP; N = 2), and Perioperative sinus endoscopy score (POSE; N = 2). Meta-regression assessed correlations between NP grading systems and SNOT-22, nasal congestion scores, total nasal symptom scores (TNSS), and Smell Identification Test-40 (SIT40). None of the NP grading systems correlated significantly with any symptom, QOL or olfactory metric. In intervention studies of surgery or monoclonal antibody treatment, changes in NPS scores did not correlate with any patient reported outcome measure (PROM) or olfactory outcomes.

Conclusion: Current NP endoscopic scoring systems are not associated with PROMs such as SNOT-22, nasal congestion scores, and TNSS as well as objective measures of olfaction. NP grading systems with improved clinical utility are needed.

Key words: endoscopic polyp scores, Lund-Kennedy, Meltzer, SNOT-22, SIT40

Introduction

Nasal polyps (NPs) are commonly seen and treated by rhinologists and are typically visualized on endoscopy. Their severity/grading is either described based on their location or size and then graded in a standardized fashion. In addition to computerized tomography, endoscopic grading is the current objective measure of chronic rhinosinusitis (CRS) severity. With the growing emphasis on evidence-based medicine and treatment outcomes, validated and simple grading systems are needed to document patient impact and subsequent response to medical or surgical interventions.

One of the first endoscopic nasal polyp grading systems, the Lund-Kennedy endoscopic score (LKES), was proposed in 1995⁽¹⁾. The LK score is based on five domains: scarring, crusting, edema, polyps, and discharge. It was initially designed for patients who have undergone endoscopic sinus surgery (ESS) but has been applied to unoperated patients as well⁽²⁾. Of the five domains, the most objective metric is NP size (LK-NP). Many different polyp grading systems have been created in the last 3 decades in attempts to improve upon the LK-NP system and endoscopic polyp grading is now a primary outcome measure

for pharmacologic studies^(3,4). Modified systems include, but are not limited to, the Perioperative Sinus Endoscopic (POSE) score⁽⁵⁾, the Discharge, Inflammation, Polyp/edema (DIP) score⁽⁶⁾, modified Lund-Kennedy (mLK) score⁽²⁾, Meltzer score⁽⁷⁾, Nasal Polyp Score (NPS, sometimes referred to a total polyp score [TPS])⁽⁸⁾, Olfactory Cleft Endoscopy Score (OCES)⁽⁹⁾ and Lildholdt polyp scale⁽¹⁰⁾.

Investigation into the degree of correlation of these varied NP scoring systems to patient-reported outcome measures (PROMs) has not been well-described in the literature, nor has any pooled data been reported for the LK-NP scoring system. Given the increased emphasis of NP grading as a primary outcome in prospective pharmacologic studies, we aimed to systematically review the literature to compile data on all endoscopic NP scoring systems that have been used and examine their correlations to PROMs and olfactory measures.

Materials and methods

Information sources and search strategy

The study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement⁽¹¹⁾. A comprehensive search was performed in the following 4 databases: PubMed (U.S. National Library of Medicine, National Institutes of Health), Scopus (Elsevier), Cochrane Library (Wiley), and CINAHL (EBSCO). The search strategies used a combination of subject headings (e.g., Mesh in PubMed) and keywords for the following concepts and/or keywords: Lund-Kennedy, Meltzer, polyp grading, polyp score, nasal, and olfactory cleft endoscopy. The PubMed search strategy was modified for the other 3 databases, replacing Mesh terms with appropriate subject headings, when available, and maintaining similar keywords. The search strategies for each database are detailed in Appendix 1.

The databases were searched from inception through August 2nd, 2021, without filters or limits. Only studies describing nasal endoscopy polyp scores, PROMs and olfaction scores were included. Nonhuman studies, case reports, non-journal publications (editorials, commentaries, etc.) and review articles were excluded. Lastly, articles with duplicate data from other studies were included only once, with the most detailed data included. To identify additional articles, the reference lists of relevant articles were hand searched, as well as citing articles.

Study selection

References were exported into the review management software, Covidence (Veritas Health Innovation, Melbourne, Australia), for study selection. Two reviewers (S.S.J, T.C.) independently screened all titles and abstracts. When a disagreement occurred, the relevant articles were discussed between the reviewers

until consensus was reached. Following the same process, two reviewers (S.S.J, T.C.) then independently screened full-text articles with conflicts being resolved by way of discussion. Two authors (S.S.J., T.C.) searched the reference lists of the included publications to identify additional articles. Articles were critically appraised to assess level of evidence using the Oxford Center for Evidence-Based Medicine criteria.

Quality and risk of bias assessment

Risk of bias was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions, version 6.2⁽¹²⁾. Specifically, the ROBINS-I (Risk of Bias in Nonrandomised Studies) tool was used because this systematic review evaluated nonrandomized studies⁽¹³⁾. Two authors (S.S.J, T.C.) performed a pilot assessment on 3 studies to check for consistency of assessment. Both then performed independent risk assessments on the remaining studies. All disagreements were resolved once both authors came to a consensus. Risk of bias items for non-randomized trials included bias due to confounding, in selection of participants into the study, in classification of interventions, due to deviation from intended outcomes, due to missing data, in measurement of outcomes, and in selection of reported results. Risk of bias items for randomized trials included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcomes assessment, incomplete outcome data, selective reporting, and other bias. The risk of bias for each aspect was graded as low, unclear, or high.

Data collection process and data items

Data extracted from studies included author, publication year, country where study was conducted, patient demographics (i.e., age, sex), and comorbidities. Various outcome data that was extracted included endoscopy polyp scores (e.g., Lund-Kennedy with nasal polyp domain, Meltzer, NPS, Lilholdt, etc. (Table 1)), PROMs (Sinonasal Outcomes Test [SNOT-22]⁽¹⁴⁾, Total Nasal Symptom Score [TNSS]⁽¹⁵⁾, and nasal blockage score, etc.), and olfaction scores (University of Pennsylvania Smell Identification Test [SIT40]⁽¹⁶⁾).

Statistical analysis and synthesis of results

To determine associations between endoscopy polyp scores (Lund-Kennedy, Meltzer, NPS, Lilholdt, etc.) and PROMs as well as olfaction (e.g., SNOT-22, TNSS, SIT40), we used meta-regression (also known as meta-analysis regression) using stratified summary estimates, with SEs, from each study. Meta-regression is a meta-analysis technique that relates statistical heterogeneity between study effect sizes to variables available in the studies by use of regression-based techniques^(17,18). For each meta-regression analysis, we calculated r (correlation coefficient with 95% confidence interval), R^2 and residual I^2 . R^2 describes the between-study variance explained by the included covariates

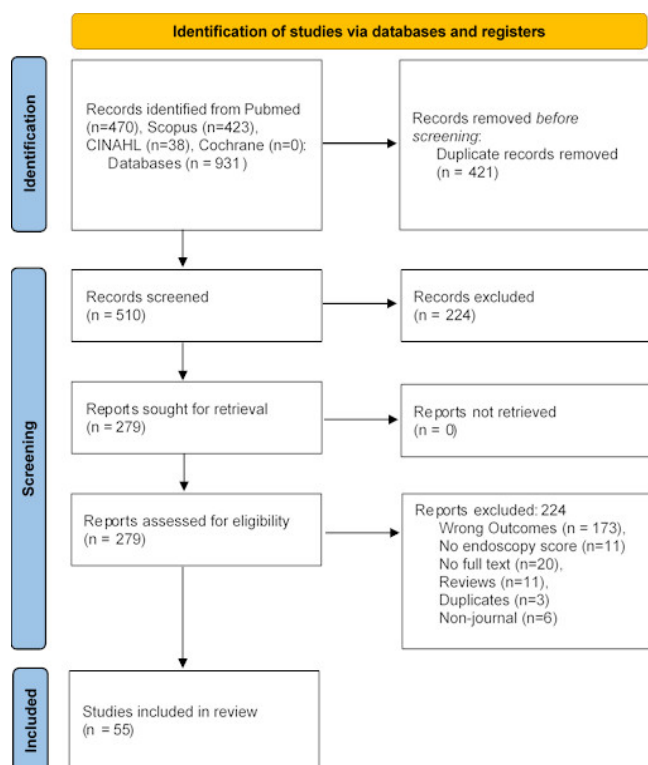


Figure 1. Flow diagram of study selection followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

and I^2 describes the proportion residual of between-study variation explained by heterogeneity versus sampling variation. A P value of <0.05 was used to indicate a statistically significant difference for all statistical tests. Finally, the Egger test was performed for further assessment of risk of publication bias⁽¹³⁾. Potential publication bias was evaluated by visual inspection of the funnel plot. In a funnel plot, treatment effect is plotted on the horizontal axis and the standard error is on the vertical axis⁽¹⁹⁾. The vertical line represents the summary estimate derived using fixed-effect meta-analysis. Two diagonal lines represent (pseudo) 95% confidence limits (effect ± 1.96 standard error) around the summary effect for each standard error on the vertical axis. These show the expected distribution of studies in the absence of heterogeneity or selection bias. In the absence of heterogeneity, 95% of the studies should lie within the funnel defined by these diagonal lines. Publication bias results in asymmetry of the funnel plot. Fifty-five unique studies were included for final analysis.

Results

Search results

Of 931 initially identified articles, 510 underwent title and abstract screening. This process eliminated 224 articles, leaving 286 for full-text review. Fifty-five studies^(2,20-73) were included for final analysis (Figure 1) of Lund-Kennedy (LK-NP) polyp scores (N

= 6), Meltzer scores (N = 6), Nasal polyp scores (NPS; N = 19), Total polyp score (TPS; N=8) Lilholdt scores (N = 8), Olfactory cleft endoscopy score (OCES; N=4), Discharge, inflammation, polyp/edema score (DIP; N = 2), and Perioperative sinus endoscopy score (POSE; N = 2).

Overall study characteristics

Table 2 provides an overview of all included studies. Each study's level of evidence was assessed according to the 2011 Oxford Center for Evidence-Based Medicine criteria⁽⁷⁴⁾. Evidence in 8 studies were level 4, in 25 studies were level 3, and in 22 studies were level 2. Critical appraisal of studies indicated an acceptably low risk of bias for most included studies (Figures 2A and 2B). Potential sources of bias were most pronounced in selective reporting in the randomized studies. Most nonrandomized studies were considered low risk, with greater potential for bias regarding participant selection and bias due to missing data. A funnel plot with Egger's test (-1.73 , $p=0.08$) demonstrated all studies were within the funnel except for one with no asymmetry, suggesting little publication bias (Supplement 1).

The fifty-five included articles^(2,20-73) consisted of a total of 6,375 patients with an endoscopy polyp score and either PROMs or olfaction scores. The pooled mean age was 47.9 (11.6) years with 3,621 (58.9%) male and 2,530 (41.1%) female patients. There appears to be some reporting differences of comorbidities and the following are listed as reported by the original studies: 132 (2.1%) had diabetes mellitus, 311 (4.9%) had allergic rhinitis, 1431 (22.4%) had asthma, 189 (3.0%) had aspirin intolerance, 713 (11.2%) had aspirin exacerbated respiratory disease (AERD), 552 (8.7%) had allergy, 423 (6.6%) had history of smoking, and 2,625 (41.2%) had prior sinus surgery.

Correlation between endoscopic polyp scores and PROMs/olfaction

Meta-regression was performed for the NP score and PROMs/olfaction pairings with at least three data points. Due to the heterogeneity of the data, only 30 articles were included in the meta-analyses. The following correlations were examined: LKES vs. SNOT-22, LK-NP vs. SNOT-22, Lildholdt vs. SNOT-22, NPS vs. SNOT-22, NPS vs. nasal congestion or obstruction score, NPS vs. TNSS, NPS vs. SIT40.

Most of the endoscopy polyp scores did not correlate strongly with PROMs or olfaction scores, except for one pairing between Meltzer score and SNOT-22. This pairing showed significant negative correlation where better polyp scores were associated with worse SNOT-22 scores. These pairings were obtained from three studies^(32,43,49) (Figure 3A). However, data points from one study⁽⁴⁹⁾ were removed because the polyp grades listed in the results were based on a different grading system than described

Table 1. Overview of Nasal Endoscopy Scoring Systems (polyp specific scoring for each side)

Scoring System	Grade	Description
Lund-Kennedy score (LKES)	Polyp (LK-NP)	
	0	Absent
	1	Confined to middle meatus
Meltzer score	2	Beyond middle meatus
	0	No polyps
	1	Small polyps in the middle meatus/edema
	2	Blocked middle meatus
	3	Polyps extending beyond middle meatus, without complete obstruction
TPS/TNEPS/NPS/Gevaert score	4	Massive nasal polyposis
	0	No polyps
	1	Small polyps in the middle meatus not reaching below the inferior border of the middle concha
	2	Polyps reaching below the lower border of the middle turbinate
	3	Large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle concha
OCES (polyp subdomain)	4	Large polyps causing complete obstruction of the inferior meatus
	0	None
	1	Discrete polyps partially narrowing/blocking the olfactory cleft (<50%)
Lildholt scale	2	Discrete polyps partially narrowing/blocking the olfactory cleft (>50%)
	0	No polyposis
	1	Mild polyposis (small polyps not reaching upper edge of the inferior turbinate)
	2	Moderate polyposis (medium sized polyps reaching between the upper and lower edges of the inferior turbinate)
Davos'/Mackay & Nacleiro/ Malm score	3	Severe polyposis (large polyps reaching below the lower edge of the inferior turbinate)
	0	No polyps
	1	Polyps posterior to the middle nasal turbinate
	2	Polyps inferior to the middle nasal turbinate
DIP score	3	Massive polyposis
	0	Normal mucosa
	5	Marked edema/no polyps
POSE score	10	Polyps filling nasal cavity
	Middle turbinate	
	0	Normal
	1-2	Synechia/lateralized
	Middle meatus/MMA	
	0	Healthy
	1-2	Narrowing/closure
	1-2	Maxillary sinus contents (edema or secretions)
	Polypoid change	
	1	Discernible outpouchings beginning to narrow or partly fill the cavity
	2	Discrete outpouchings fill the ethmoid cavity
	Polyposis	
	1	Extending beyond middle meatus but not to the inferior turbinate
	2	Beyond the upper border of the inferior turbinate
	1-2	Secretions

Table 2. Overview of characteristics of studies included in meta-analysis.

Study	LOE	Study design	N	Intervention of interest	NP grading	PROM/Olfaction
Aboud (2014)	3	Prospective cohort	55	Intranasal (Mometasone furoate) and systemic steroids (oral prednisone)	Lilholdt	RSDI
Adriaensen (2017)	2	RCT	81	ESS	TPS	SNOT-22
Akarcay (2010)	3	Prospective cohort	27	ESS	TPS	SNOT-22
Arancibia (2020)	3	Prospective cohort	70	ESS + systemic steroids (oral prednisone)	NPS	T5SS
Armengot-Carceller (2021)	4	Retrospective case series	23	Omalizumab	TPS	SNOT-22
Awad (2019)	3	Prospective cross-sectional	200	-	LK-NP	SNOT-20
Ayoub (2018)	2	RCT	20	ESS	LK-NP	SNOT-22
Bachert (2016)	2	RCT	60	Dupilumab	NPS	SNOT-22, SIT40
Bachert (2017)	2	RCT	107	Mepolizumab	NPS	SNOT-22
Balsalobre (2019)	4	Prospective case control	12	-	Meltzer	SNOT-22
Bartosik (2021)	3	Retrospective cohort	105		NPS	SNOT-20 GAV
Beswick (2021)	3	Prospective case series	165	ESS	LK-NP	SNOT-22
Chitguppi (2020)	4	Retrospective case series	23	-	Meltzer	SNOT-2
Detoraki (2021)	3	Prospective case series	44	Mepolizumab	TPS	SNOT-22
Detoraki (2021)	4	Prospective case series	8	Mepolizumab	TPS	SNOT-22
Ebbens (2006)	2	RCT	116	Amphotericin	NPS	RSOM31, Nasal blockage VAS
Epperson (2019)	3	Prospective cohort	64	-	Lilholdt	SNOT-22
Fruth (2013)	2	RCT	70	Aspirin	Lilholdt	German RSDI, Sniffin' Sticks
Fujieda (2021)	2	RCT	49	Dupilumab	NPS	SNOT-22, SIT40
Gevaert (2020)	2	RCT	265	Omalizumab	NPS	SNOT-22, TNSS, SIT40
Han (2021)	2	RCT	407	Mepolizumab	NPS	SNOT-22
Han (2014)	2	RCT	100	ESS	Meltzer	Nasal congestion score
Hashemian (2020)	2	RCT	40	Vitamin D	Meltzer	SNOT-22
Hashemian (2016)	2	RCT	92	Furosemide	Meltzer	SNOT-22
Hong (2018)	3	Prospective case series	47	-	NPS	TNSS
Hopkins (2021)	2	RCT	724	ESS	NPS	SNOT-22, SIT40
Huang (2019)	3	Prospective cohort	60	Topical Steroids (Budesonide)	LK-NP	SNOT-22
Kiris (2016)	2	RCT	90	Systemic Steroids (oral prednisolone) or steroid injection (triamcinolone)	NPS	TNSS
Kirtsreesakul 2012	2	RCT	114	Systemic Steroids (oral prednisolone)	NPS	TNSS
Kobayashi (2018)	2	RCT	23	Inhaled Steroids (beclomethasone dipropionate)	Meltzer	SNOT-22
Kule (2014)	3	Retrospective cohort	77	-	NPS	NOSE
Laidlaw (2021)	2	RCT	724	-	TPS	SNOT-22
Lavigne (2014)	4	Prospective case series	12	-	TPS	SNOT-22
Lechien (2020)	4	Prospective case series	16	-	OCES	SNOT-22, Sniffin' Sticks
Lee (2007)	3	Prospective cohort	60	-	NPS	Nasal obstruction VAS
Little (2021)	3	Prospective cohort	218	ESS	LK-NP	SNOT-22

Study	LOE	Study design	N	Intervention of interest	NP grading	PROM/Olfaction
Lombardo (2020)	4	Prospective case series	10	-	Lilholdt	SNOT-22
Mattos (2021)	3	Prospective case control	277	ESS	OCES	QOD-NS
Moreno-Luna (2021)	3	Prospective case control	20	-	Lilholdt	SNOT-22
Othieno (2018)	3	Prospective cohort	69	-	OCES	SNOT-22
Ow (2014)	4	Prospective case series	5	Steroid stent (Mometasone furoate)	NPS	SNOT-22
Palmer (2018)	3	Prospective cohort	223	-	Lilholdt	SNOT-22
Peric (2014)	2	RCT	80	Surgery	NPS	Nasal symptom score
Pletcher (2010)	3	Prospective cohort	8	Endoscopic placement of foam	POSE	SNOT-20
Psaltis (2014)	3	Prospective cohort	102	-	DIP, POSE	SNOT-22
Schlosser (2021)	3	Prospective case control	405	-	OCES	SNOT-22, Sniffin' Sticks, QOD-NS
Schneider (2020)	3	Retrospective cohort	122	-	TPS	SNOT-22
Shen (2019)	2	RCT	43	-	LK-NP	SNOT-22
Sher (2020)	3	Prospective cohort	705	-	Lilholdt	SNOT-22
Sindwani (2019)	2	RCT	323	-	Lilholdt	SNOT-22
Tversky (2021)	2	RCT	24	-	NPS	SNOT-22, SIT40
Vaidyanathan (2011)	2	RCT	60	Systemic Steroid (oral prednisolone)	NPS	TNSS
Vaidyanathan (2010)	3	Prospective cohort	12	Systemic Steroid (oral prednisolone)	NPS	SNOT-20
Zhang (2019)	3	Prospective cohort	40	-	LK-NP	Nasal obstruction VAS
Zhang (2017)	3	Prospective cohort	144	ESS	DIP	SNOT-22

LOE = level of evidence, N = number, NP = nasal polyp, RCT = randomized controlled trial, ESS = endoscopic sinus surgery, VAS = Visual analog scale, RSDI = Rhinosinusitis Disability Index, T5SS = Total 5-Symptom Scores, NOSE = Nasal Obstruction Symptom evaluation, LK-NP = Lund-Kennedy nasal polyp domain, SNOT-22 = Sinonasal Outcomes Test 22, SNOT-20 = Sinonasal Outcomes Test 20, SNOT-20GAV = Sinonasal Outcomes Test 20 German Adapted Version, TPS = Total Polyp Score, NPS = Nasal Polyp Score, OCES = Olfactory Cleft Endoscopy Score, RSOM31 = Rhinology Outcome tool, QOD-NS = Questionnaire of Olfactory Disorders Negative Statements, POSE = Perioperative Sinus Evaluation, SIT40 = University of Pennsylvania Smell Identification Test.

in the methods. After removal, the significance disappeared (Figure 3B). The remaining correlations were not significant.

Surgical Intervention – Correlation between change in LKES and LK-NP scores vs change in SNOT-22

Meta-regression was conducted for studies that included data regarding change in endoscopic polyp scores and change in SNOT-22. Three different studies^(31,46,75) were included in this analysis. Results show that with surgical intervention, there is not a significant correlation between mean change in LKES and mean change in SNOT22 ($r=0.36$, $p=0.56$) (Figure 4A). There was also no significance between change in LK-NP and change in SNOT-22 (Figure 4B).

Biologics Intervention - Correlation between change in NPS vs change in PROMs/olfaction

Eight studies^(24,28,33,34,38-40,44) were included in the analysis to correlate change in NPS to change in PROMs (SNOT-22, nasal congestion) and olfaction (SIT40). Four of the studies^(28,38-40) had placebo groups that were also utilized in this analysis. None of the groups yielded significant correlations (Figure 5).

Discussion

Our study represents one of the first attempts in peer-reviewed literature to quantify and consolidate the nasal polyp grading systems in predicting PROMs and olfaction measures. In our initial analysis, we correlated several different polyp grading systems with various PROMs/olfaction measures. The results were not significant. Our secondary analysis examined different interventional groups and similarly yielded no significance. If polyp size was correlated to PROMs or olfaction scores, then we should expect significant improvements in PROMs for patients who

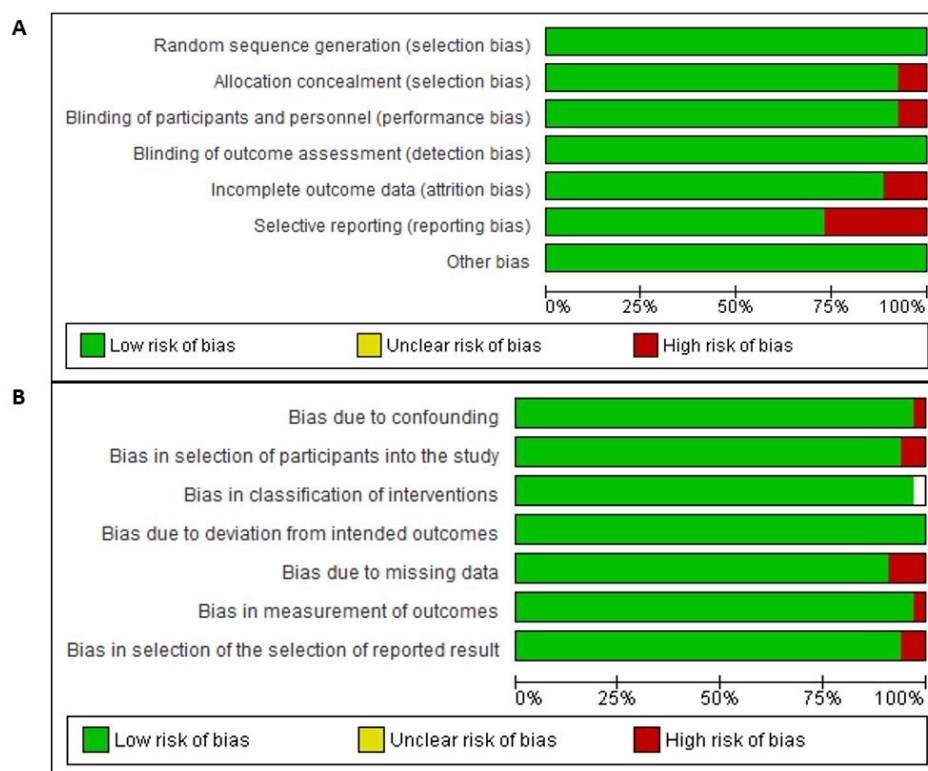


Figure 2. Risk of Bias. A) Risk of bias for randomized controlled studies. B) Risk of bias for nonrandomized studies.

underwent treatment with reduction in polyp size. However, our study again showed no significant relationship between change in polyp size and improvement in PROMs. There was also no significance in the cohort that received biologics, which target specific components of the immune system. Thus, our results highlight the shortcomings of the current nasal polyp grading systems and the complicated pathophysiologic mechanisms involved in chronic rhinosinusitis with nasal polyps.

Numerous endoscopic NP scoring systems have been described in the literature. However, discrepancies between NP scores and symptoms scores have been documented. The appearance of multiple different NP grading systems over the past 20 years is a testament to the inconsistencies and limited utility of the current systems in gauging outcomes or PROMs. This raises the question of which, if any, scoring system is the most strongly correlated with PROMs and olfaction.

The LKES has been the most widely utilized scoring system since its inception in 1995⁽¹⁾. There have been conflicting studies on the correlation between LKES and QOL measures. It has been suggested that differing conclusions may be due to functional and emotional domains of comprehensive quality of life scores like SNOT-22, which can be influenced by non-disease specific factors⁽⁷⁶⁾. Another explanation could be that though it was originally intended for use in patients with a history of sinus sur-

gery, it is commonly applied to patients outside the postsurgical population⁽²⁾. Psaltis et al. found that there was a correlation between SNOT-22 and LKES in postoperative patients, but not unoperated patients⁽²⁾. There has been little investigation into the LK-NP score specifically and its correlation to PROMs.

Attempts have been made to improve upon the LKES by changing the size of the scale of NP size grading or tailoring it to specific patient populations. In the same year, the Lildholdt score was created, which ranges from 0 to 3⁽¹⁰⁾. The following year, at an international workshop held in Davos, Switzerland, Mackay and Nacleiro presented another scale of grades 0 to 3. Their data was never officially published but was first referenced in Malm et al.⁽⁷⁷⁾. Therefore, in the literature, the scale has been called the Davos, Mackay and Nacleiro, or Malm score⁽⁷⁸⁾. In 2006, the Meltzer score was proposed, consisting of grades 0 to 4 for each side. It was designed to be reproducible and easily interpret outcome measures, making it useful for clinical trials⁽⁷⁾. The POSE score was proposed in 2007, which incorporated parameters of multiple sinuses and middle meatus and turbinate⁽⁵⁾. Though it may be more sensitive to change over time postoperatively, it has a lower test-retest reliability. Also, it cannot be used in nonsurgical patients⁽²⁾.

In 2012, the DIP score was developed by removing the scarring and crusting domains from the LKES, as well as increasing nu-

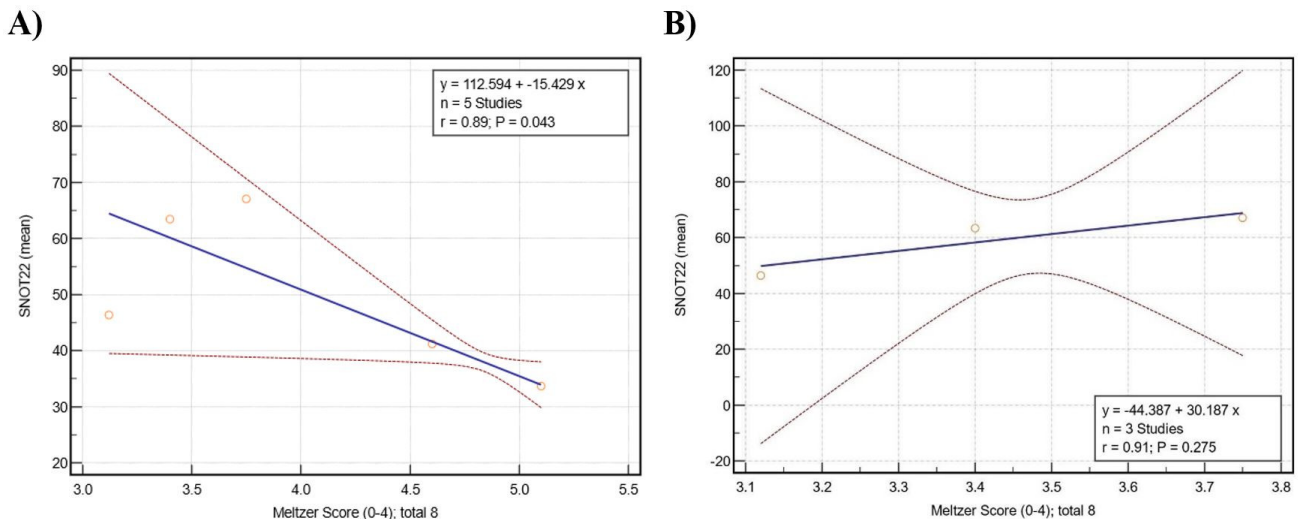


Figure 3. Correlation of Meltzer score and SNOT-22. Blue lines represent the best fit line of regression. The red lines above and below the blue lines represent the confidence intervals (95%). “y” is the equation for best fit line of regression, “r” indicates correlation, and “P” indicates significance. A) Graph shows that there is strong, negative correlation ($r=0.89$) between SNOT22 and Meltzer score with significance ($p=0.043$). However, this graph includes two data points from a study that had a different polyp grading system than described in the methods. B) After the two data points were removed, correlation between SNOT-22 and Meltzer score was very strong ($r=0.91$), but there was no significance ($p=0.275$).

merical points for each remaining domain. These changes were implemented in order to increase applicability to preoperative patients and sensitivity to changes in disease severity^(2,6). In a proposal for a modified LKES in 2012, the scarring and crusting domains were eliminated but the familiar numerical points of the LKES preserved⁽²⁾. Gevaert et al. introduced the Total Nasal Endoscopic Polyp Score (TPS or TNEPS), sometimes simply referenced as Nasal Polyp Score (NPS), in 2013, which was graded from 0 to 4 on each side⁽⁸⁾. Most recently in 2016, Soler et al. presented the OCES. While similar in domains and grading to the LKES, it focuses on the olfactory cleft specifically, whereas other scoring systems involve the middle meatus or sinuses. As such, it may be the most useful for quantifying olfactory outcomes⁽⁹⁾.

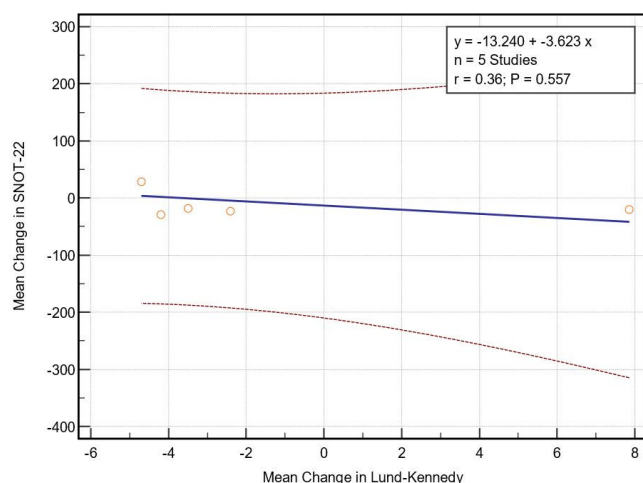
While many of the current grading systems are meant to provide objective, reproducible data, grading can be quite subjective. A 2017 study by Zhang et al. showed that across different endoscopic scoring systems, the intraclass correlation coefficients (ICC) were moderate (0.65-0.68)⁽⁶³⁾. ICC indicates the level of agreement between two or more clinicians when using the same scoring systems. For LKES specifically, the ICC dropped from 0.67 to 0.56 if the patients previously had surgery for polyps. This means that depending on the surgical history of the patient, the results of the LKES system may fluctuate to a greater degree across different clinicians. This subjectivity in the scoring system may be the reason for a lack of correlation found between these scoring systems and PROMs.

As it was alluded to earlier, the QOL scoring measures may

be another reason for the lack of correlation. For instance, in SNOT-22, it is reasonable to expect that NP grading would likely correlate with nasal specific symptoms such as nasal blockage, runny nose, postnasal discharge, etc. However, it seems unlikely that NP grading would correlate with SNOT-22 categories such as cough, ear fullness, dizziness, etc. As a result, even though endoscopic polyp grading may correlate better with nasal specific symptoms the overall SNOT-22 scores may not see such significant changes or correlations. Conversely, the opposite can also hold true. It has been shown that patients who take biologics for their symptomatic nasal polyps have significant improvement in their SNOT-22 and SIT40 scores despite maintaining a significant polyp burden⁽⁷⁹⁻⁸¹⁾. Thus, it seems likely that other factors besides polyp size alone impact PROMs and olfaction. It is also possible that there are multiple interrelated factors where polyp size is only a small part of what contributes to PROMs and olfaction.

It is also possible that the current polyp grading systems are simply just not detailed enough. For instance, the grading of polyps is based on ordinal values from 0-4, however this scale is not proportional, ie a polyp of size 2 is not 50% of a grade 4 polyp. In addition, these grades are determined based upon the location of the polyp and/or the most inferior extent and does not properly consider the three-dimensional aspect of the sinonasal cavity. If these grading systems became continuous outcomes or took volume into account instead of being represented as categorical outcomes, we may find better correlation. It is also possible that correlations are non-linear. Patients with “0 or 1” polyp grade usually experience very little to no symptoms while

A) Lund Kennedy Endoscopic Score (LKES)



B) Lund Kennedy Nasal Polyp Score (LK-NP)

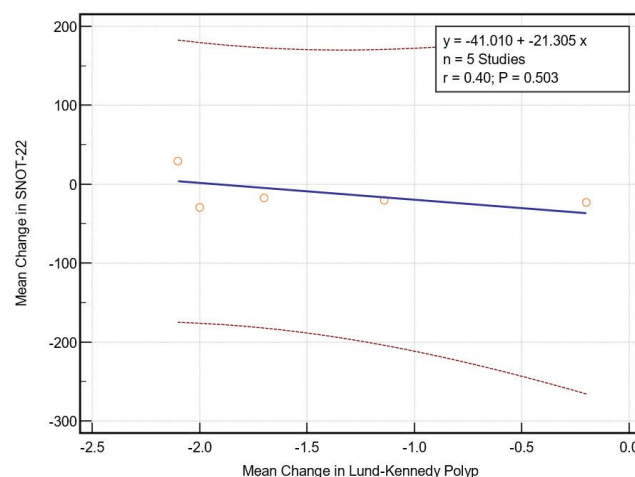


Figure 4. Surgical Intervention – Mean change in Lund-Kennedy Endoscopic Score (LKES) and Lund-Kennedy Nasal Polyp (LK-NP) Score correlated to mean change in SNOT-22. Blue lines represent the best fit line of regression. The red lines above and below the blue lines represent the confidence intervals (95%). “y” is the equation for best fit line of regression, “r” indicates correlation, and “P” indicates significance. A) Graph represents correlation of mean change in SNOT-22 with mean change in LKES. This graph shows that there is weak correlation ($r=0.36$) with no significance ($p=0.557$). B) Graph is for the mean change in only the nasal polyp score component of LKES correlated with mean change in SNOT-22. There is mild correlation ($r=0.40$) with no significance ($p=0.903$).

patients with a polyp grading of “4” usually experience severe symptoms. Thus, there may be a critical threshold as NP extend out of the middle meatus that begins to cause symptoms in a more linear fashion.

Limitations

One limitation in the study was our small sample size for each specific staging system. Although many studies included polyp scoring systems and PROMs/olfaction scores, actual sample size ended up being smaller than expected because of heterogeneity. Across fifty-five studies included in our study, only four studies had data for our analysis in correlating LK-NP scores with SNOT-22. This continued to occur across different NP scoring systems which reduces the power of our results, especially in a meta-regression analysis. Normally, meta-regressions utilize at least ten data points, but in our study, we could only conduct this analysis with three to eight data points.

Another limitation to our study was our analyses involving treatment protocols. Although surgical interventions were mostly uniform, biologic treatment protocols were not. In our analyses, we combined all biologics (e.g., dupilumab, omalizumab, mepolizumab) together because sample sizes were too small to analyze therapies individually. It is possible that with more data, analyses of an individual biologic type may yield significant results or different correlations. Furthermore, maintenance therapies were not well reported in the included studies, and significant heterogeneity was noted amongst the few reported.

As a result, this introduces another confounding variable in the interventional analyses.

Another possible source of heterogeneity may be amongst the patients that were included in the meta-analysis. Even though all the patients had polyps, some patients had subtypes of CRSwNP that are known to have more severe symptoms such as AERD or allergic fungal rhinosinusitis (AFRS). There might be a stronger correlation between endoscopy scores and PROMs/olfaction if a homogenous population with a single subtype of CRSwNP were to be studied.

Future directions

Future studies include developing systems that quantify polyp sizes with less subjectivity and improved nuance. For instance, a system that considers shape and location of the polyp and not just its confinement within the different meatus may provide more consistency in assessment amongst providers. Additionally, continuous measures for example, precise volumetric measures and/or use of artificial intelligence may provide better objectivity and potential for correlations. These improvements would hopefully lead to universal utility both for clinical practice, as well as for researchers.

Endotype is another example of ‘other’ factors that may influence symptom severity. Traditionally, CRS is classified by phenotype (CRSwNP vs. CRSsNP), but more recently, classification by disease endotype, based on inflammatory cell predominance,

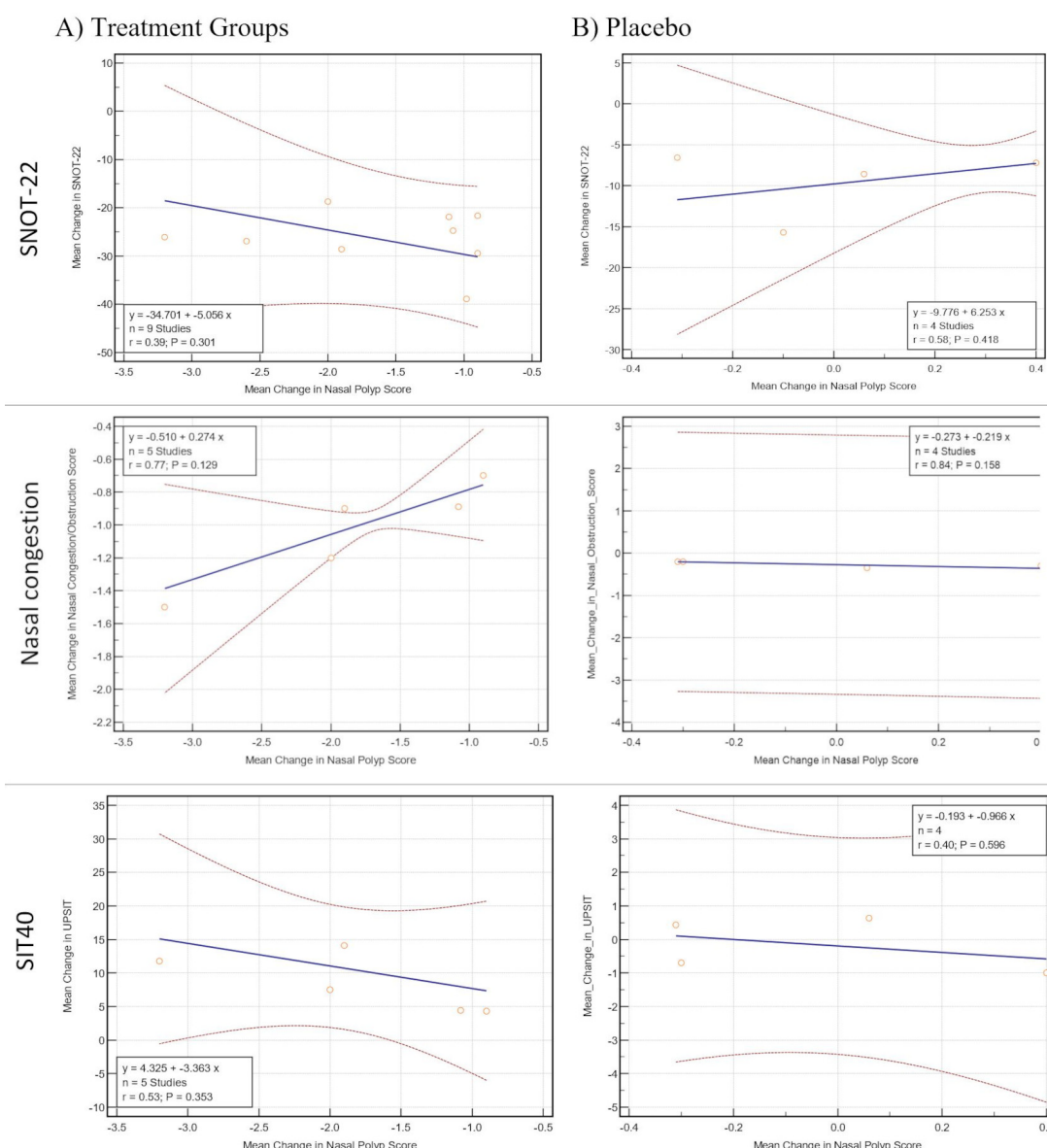


Figure 5. Biologics Intervention – Correlation between change in nasal polyp score (NPS) and patient-reported outcome measures (PROM)/olfaction (i.e. SNOT-22, Nasal congestion, SIT40). Blue lines represent the best fit line of regression. The red lines above and below the blue lines represent the confidence intervals (95%). “y” is the equation for best fit line of regression, “r” indicates correlation, and “P” indicates significance. Column A represents patients who received biologics while column B represents patients who received placebo. No significance was found for all correlations. SNOT-22) Correlation between mean change in SNOT-22 and mean change in NPS was mild ($r=0.39$) in the treatment groups and moderate ($r=0.58$) in the placebo group. Nasal congestion) Correlation between mean change in nasal congestion score and mean change in NPS was strong for both treatment and placebo group ($r=0.77$ and 0.84 , respectively). SIT40) Correlation between mean change in SIT40 and mean change in NPS was moderate for the treatment group and mild for the placebo group ($r=0.53$ and 0.40 , respectively).

has been proposed⁽⁸²⁾. Eosinophils, in particular, have been associated with olfactory loss⁽⁸²⁻⁸⁴⁾. Eosinophilic CRS has been correlated with greater clinical severity and eosinophilic nasal polyps with mixed pattern inflammation tend to have greater cytokine burden^(85,86). As mentioned previously, specific polyp locations should be considered, since removal of polyps in the olfactory cleft has been shown to improve olfactory outcomes⁽⁸⁷⁾. Environmental or occupational exposures may also contri-

bute to disease severity. Though a systematic review in 2015 was inconclusive on most exposures, several studies and literature reviews have noted the association of cigarette smoke to worse CRS symptoms and outcomes⁽⁸⁴⁾. The addition of cannabis to tobacco smoke appears to worsen the severity of outcomes than tobacco smoke alone^(88,89). Lastly, history of frequent oral steroids and antibiotics use and other comorbidities, such as asthma, have been significantly correlated with higher SNOT-22

scores and more severe CRS⁽⁹⁰⁾.

Overall, there are multiple factors that might contribute to the pathogenesis of chronic rhinosinusitis with polyps and provide rationale as to why polyp size may not correlate with PROMs. Furthermore, future studies should examine if markers of inflammation and disease severity other than nasal polyp size may better predict symptom severity.

Conclusion

The current endoscopic scoring systems poorly predict PROMs and olfaction measures such as SNOT-22, nasal congestion scores, TNSS, and SIT40. A more predictive and reliable polyp grading system is needed.

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Authorship contribution

SSJ, TC, and RJS conceived the original idea. This was also discussed with TSE and SAN. Eventually, all authors discussed and agreed with the main focus and ideas of this paper. SSJ and TC developed the initial search strategies, inclusion, and exclusion criteria. These were further discussed with RJS before proceeding with study selection and data extraction which was performed by SSJ and TC. SAN performed the data analysis and results were discussed among all the authors. The main text of the paper was written by SSJ and TC and subsequently edited by RJS, TSE, and SAN. SSJ led the project with significant help from TC.

Conflict of interest

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SUPPLEMENTARY MATERIAL

Database	Search Terms	Date/Limits/Results
Pubmed	"Olfactory cleft endoscopy" OR "Lund-Kennedy" OR "Lund Kennedy" OR ("Meltzer" AND polyp) OR ("score" AND "polyp" AND ("nose" OR "nasal" OR "sinus" OR Johansen))	Date: 8/2/2021 Limits: No limits Results: 470
SCOPUS	TITLE-ABS({olfactory cleft endoscopy} OR {Lund-Kennedy} OR {Lund Kennedy} OR ({Meltzer} AND polyp) OR ({score} AND {polyp} AND ({nose} OR {nasal} OR {sinus} OR {Johansen})))	Date: 8/2/2021 Limits: No limits Results: 423
CINAHL	"Olfactory cleft endoscopy" "Lund-Kennedy" OR "Lund Kennedy" "Meltzer" AND polyp "score" AND "polyp" "nose" OR "nasal" OR "sinus" OR Johansen #3 AND #4 #1 OR #2 OR #3 OR #6	Date: 8/2/2021 Limits: No limits Results: 38
Cochrane	"Olfactory cleft endoscopy" OR "Lund-Kennedy"	Date: 8/2/2021 Limits: No limits Results: 0