

Brief Report

Not peer-reviewed version

Endoscopic Features of Chronic Rhinosinusitis in Patients with Gastroesophageal Reflux Disease

[Kalamkas Sagandykova](#)*, Nataliya Papulova, Talapbek Azhenov, Aliya Darbekova, Bayan Aigozhina, [Jerome R. Lechien](#)

Posted Date: 5 June 2024

doi: 10.20944/preprints202406.0239.v1

Keywords: Endoscopic picture; Laryngopharyngeal reflux; Rhinosinusitis; Nasopharyngeal reflux; The Reflux Symptom Index; The Reflux Symptom Score



Preprints.org is a free multidiscipline platform providing preprint service that is dedicated to making early versions of research outputs permanently available and citable. Preprints posted at Preprints.org appear in Web of Science, Crossref, Google Scholar, Scilit, Europe PMC.

Copyright: This is an open access article distributed under the Creative Commons Attribution License which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Brief Report

Endoscopic Features of Chronic Rhinosinusitis in Patients with Gastroesophageal Reflux Disease

Kalamkas T. Sagandykova ^{1,2,*}, Nataliya M. Papulova ², Talapbek M. Azhenov ², Aliya Darbekova ³, Bayan Ch. Aigozhina ² and Jerome R. Lechien ^{4,5,6}

¹ "University Medical Center" Corporate Fund, Astana, Kazakhstan

² NpJSC "Astana Medical University", Astana, Kazakhstan; azhenov.t@amu.kz

³ Medical Center Hospital of the President's affairs Administration of the republic of Kazakhstan, Astana, Kazakhstan; darbekova@bmc.mcup.kz

⁴ Laryngopharyngeal Reflux Study Group of Young-Otolaryngologists of the International Federations of Oto-Rhino-Laryngological Societies (YO-IFOS); jerome.lechien@umons.ac.be

⁵ Department of Otolaryngology-Head and Neck Surgery, Foch Hospital, Paris, France

⁶ School of Medicine, University Paris Saclay, 91190 Paris, France

* Correspondence: kalamkas.sagandykova@umc.org.kz; Tel.: +7-702-215-77-51

Abstract: Chronic rhinosinusitis (CRS) is a complex inflammatory condition affecting the nasal and paranasal sinus mucosa. Gastroesophageal reflux disease (GERD) has been implicated as a potential exacerbating factor in CRS, but the specific endoscopic features of nasopharyngeal pathology in this context remain poorly understood. *Background and Objectives:* CRS is a multifactorial disease with various underlying etiologies, including inflammation, anatomical factors, and environmental triggers. While GERD has been suggested as a potential contributor to CRS, the specific endoscopic features indicative of nasopharyngeal pathology in CRS patients with GERD symptoms have not been clearly elucidated. Our aim is to identify specific endoscopic features of nasopharyngeal pathology in patients with CRS associated with GERD symptoms, and to propose a method for assessing the influence of GERD on the mucosal layer of the nose and nasopharynx. *Materials and Methods:* We conducted a cross-sectional observational study involving 521 adult patients presenting with symptoms suggestive of CRS. From this cohort, 95 patients with the highest scores on the Reflux Symptom Index (RSI) and Reflux Symptom Score-12 (RSS-12) questionnaires were selected as the main group. Endoscopic examinations were performed to assess the nasal and nasopharyngeal mucosa. *Results:* Our study revealed significant alterations in the nasopharyngeal mucosa of patients with CRS associated with GERD symptoms. Increased vascularity of the nasopharyngeal mucosa was observed in 91 patients (95.7%), while hypertrophy was noted in 83 patients (87.4%). Mucus was present in the nasopharynx of 77 patients (81.1%), exhibiting varying characteristics of color and consistency. Asymmetric hypertrophy of the oropharyngeal mucosa was noted in 62 patients (65.3%). *Conclusions:* We propose a method for assessing the influence of GERD on the mucosal layer of the nose and nasopharynx, which may aid in diagnostic and management decisions. Further research is warranted to explore the potential impact of GERD symptoms on the course and severity of CRS exacerbations.

Keywords: endoscopic picture; laryngopharyngeal reflux; rhinosinusitis; nasopharyngeal reflux; the reflux symptom index; the reflux symptom score

1. Introduction

Adult chronic rhinosinusitis is an inflammation of the mucosal layer of the nose and paranasal sinuses, characterized by two or more symptoms, one of which must be either nasal congestion or nasal discharge (anterior or posterior). Additional symptoms may include facial pain and/or pressure and a decreased or lost sense of smell lasting for 12 weeks or more. Diagnostic criteria include

endoscopic signs such as nasal polyps, mucopurulent discharge predominantly from the middle nasal passage, swelling/obstruction of the mucosa predominantly of the middle nasal passage, and/or CT changes such as mucosal changes in the osteomeatal complex and/or sinuses [1].

Numerous factors can cause and exacerbate chronic rhinosinusitis, making it refractory to optimized treatment. These factors include genotypic or phenotypic mucosal changes, scarring and synechiae, allergies, smoking, and gastroesophageal acid reflux [2]. The current definition of actionable gastroesophageal reflux disease (GERD) requires convincing evidence of reflux-related pathology, demonstrated by endoscopy and/or abnormal reflux monitoring using the Lyon Consensus thresholds, along with compatible bothersome symptoms. While typical bothersome symptoms alone may justify antisecretory drug trials, esophageal testing is recommended for all other symptom categories and for patients who do not respond to proton pump inhibitors (PPIs). This testing should be conducted prior to invasive GERD treatment or long-term medical therapy [3]. Changes in the laryngeal mucosal layer due to laryngopharyngeal reflux were first described and systematized in 2001 by Belafsky et al. [4]. In 2020, Lechien et al. further detailed the endoscopic appearance of the larynx under the influence of laryngopharyngeal reflux by describing changes on the pharyngeal side [5]. In 2022, Zelenik et al. identified a relationship between hypertrophy of the inferior turbinate and extraesophageal reflux [6].

Endoscopic findings of laryngopharyngeal reflux have been well-documented, but the specific endoscopic features of nasopharyngeal pathology in CRS patients with GERD symptoms remain poorly understood. Previous studies have highlighted the association between extraesophageal reflux and nasal mucosal hypertrophy, underscoring the need for further investigation into the relationship between GERD and CRS.

The aim of our study is comprehensively assess the endoscopic features of the nose and nasopharynx in patients with chronic rhinosinusitis who also exhibit symptoms of gastroesophageal acid reflux disease. Our specific objective is to detect any aberrations in the endoscopic presentation of chronic rhinosinusitis associated with symptoms of acid gastroesophageal reflux disease. We anticipate that this investigation will contribute to enhanced patient care by facilitating more precise diagnostic and therapeutic strategies, potentially mitigating the occurrence and duration of chronic rhinosinusitis exacerbations.

2. Materials and Methods

Local Ethical Commission of “Astana Medical University” NpJSC approved the study protocol (LCB NpJSC AMU #13).

Patient and Setting

The research method is a cross-sectional observational study design. A total of 521 adult patients from September 2023 to February 2024 with chronic rhinosinusitis were screened and treated at the University Medical Center Corporative Fund (UMC CF) and Multidisciplinary Hospital #1 in Astana, Kazakhstan. The patients met the clinical definition of chronic rhinosinusitis, characterized by symptoms caused by an inflammatory process in the nasal and paranasal sinus mucosa. Clinical symptoms included nasal congestion, nasal discharge, and/or facial pain/pressure, with or without a decreased or lost sense of smell lasting more than 12 weeks. Diagnosis was confirmed through computed tomography (CT) and endoscopic imaging.

All patients were examined using endoscopic diagnostic methods during the remission period of chronic rhinosinusitis and before starting anti-reflux treatment for gastroesophageal reflux disease (GERD). GERD symptoms were confirmed in all patients using endoscopic diagnostic methods. Standardized questionnaires were administered to all patients with confirmed chronic rhinosinusitis and GERD symptoms.

To determine the regularity of changes in the nasal and nasopharyngeal mucosa, we selected patients with the highest scores on the Reflux Symptom Index (RSI) (>20) and Reflux Symptom Score-12 (RSS-12) (>130). Patients who smoked, had active seasonal allergies or asthma, a history of

laryngeal cancer, or were pregnant were excluded from the study, resulting in a final group of 95 patients.

The control group comprised 41 patients with chronic rhinosinusitis but without GERD symptoms, and 10 patients without any signs of chronic rhinosinusitis or GERD symptoms.

Standardized Questionnaires

The Reflux Symptom Index (RSI), a 9-item self-administered questionnaire developed by Belafsky et al. (2002), was used to document the presence and degree of symptoms of laryngopharyngeal reflux. The maximum score on the RSI is 45 [7].

The Reflux Symptom Score (RSS) is a 12-item self-administered tool used to diagnose and monitor laryngopharyngeal reflux (LPR) and its impact on quality of life. The maximum score is 300 [8].

Endoscopic Assessment

A flexible endoscope was used to perform an endoscopy of the nasal cavity and nasopharynx. The condition of the lower nasal turbinate was assessed according to the Camacho classification [9,10], which grades the total airway space occupied by the turbinate as follows:

- Grade 1: 0%–25%
- Grade 2: 26%–50%
- Grade 3: 51%–75%
- Grade 4: 76%–100%

Additionally, the condition of the nasopharyngeal mucosa and the Eustachian tube junction was evaluated.

3. Results

Description

Table 1 presents the descriptive statistics of the groups under consideration in terms of the sex of the subjects. In the main group, 48.4% of participants were male, while 51.6% were female. Control Group 1 had a higher proportion of males, accounting for 56.1% of participants, whereas Control Group 2 had the highest proportion of males, with 60.0%.

Table 1. Descriptive Statistics of Group Structure by Sex.

	Group		
	main	Control 1	Control 2
Male (n=75)	46	23	6
% in group	48.4	56.1	60
Female (n=71)	49	18	4
% in group	51.6	43.9	40

Description

Table 2 presents the descriptive statistics for age, RSS-12, and RSI by group. In the main group, the mean age was 48.9 years, with a confidence interval (CI) of ± 2.8 years. The youngest participants were in Control Group 2, with a mean age of 32.5 years and a CI of ± 4.0 years.

Table 2. Descriptive Data on Age, RSS-12, and RSI by Group.

	Main		Control 1		Control 2	
	Mean	CI	Mean	CI	Mean	CI
Age	48.9	2.8	36.8	3.2	32.5	4.0

RSS-12	29.0	1.2	9.8	0.8	7.6	1.4
RSI	186.8	7.4	14.5	1.4	14.0	1.8

For the RSS-12 score, the main group had a mean score of 29.0, with a CI of ± 1.2 , while Control Group 1 had a mean score of 9.8 with a CI of ± 0.8 , and Control Group 2 had a mean score of 7.6 with a CI of ± 1.4 .

Regarding the RSI score, the main group had a notably high mean value of 186.8, with a CI of ± 7.4 , whereas Control Group 1 and Control Group 2 had mean scores of 14.5 and 14.0, respectively, with CIs of ± 1.4 and ± 1.8 .

Description

Table 3 presents the results of comparing the means of age, RSS1, and RSI1 between groups based on sex, race, and observation group. The p-value indicates whether the difference between the means is statistically significant. A p-value greater than 0.05 suggests that the means are not significantly different.

Table 3. Descriptive data on age, RSS-12 and RSI by group.

		Age	p-value ¹	RSS-12	p-value ¹	RSI	p-value ¹
		Middle		Middle		Middle	
sex	Male	43.23 (CI 3.29)	0.252	22.36 (CI 2.60)	0.641	125.39 (CI 21.47)	0.828
	Female	45.65 (CI 3.11)		21.87 (CI 2.34)		127.76 (CI 19.32)	
Race	M	44.75 (CI 2.77)	0.809	22.80 (CI 2.21)	0.075	128.07 (CI 18.14)	0.099
	E	43.49 (CI 3.89)		20.39 (CI 2.56)		122.63 (CI 22.15)	
Group	main	48.94 (CI 2.77)	0.000 ²	28.96 (CI 1.20)	0.000 ²	186.76 (CI 7.40)	0.000 ²
	Control 1	36.78 (CI 3.19)		9.83 (CI 0.82)		14.46 (CI 1.42)	
	Control 2	32.50 (CI 3.99)		7.60 (CI 1.44)		14.00 (CI 1.85)	

¹ Mann-Whitney U test for independent groups. ² Kraskal-Wallis criterion for independent groups.

For instance, the difference between the RSS1 means for men (22.36) and women (21.87) is not statistically significant (p=0.641). However, significant differences were observed in the mean ages among the main, control 1, and control 2 groups, indicating that the mean ages in these groups are significantly different with a 95% confidence level.

The Mann-Whitney U criterion for independent groups, noted as 1, was applied to determine significance. This non-parametric statistical criterion compares two independent samples on the level of a quantitatively measured characteristic. A smaller p-value suggests more reliable differences between the values of a parameter in the samples.

The Kruskal-Wallis criterion method for independent groups, noted as 2, was used to determine if there is a statistically significant difference between the medians of three or more independent groups, specifically the ‘main’, ‘control 1’, and ‘control 2’ groups. This non-parametric test is chosen due to the violation of the assumption of normality of the data distribution in the groups. If the p-value is greater than 0.05, it indicates that there is no statistically significant difference between the medians.

During endoscopic examination of the nose and nasopharynx, we noted distinct alterations in the mucosa of the posterior parts of the nasal cavity, particularly at the posterior end of the inferior nasal concha, in patients with chronic rhinosinusitis associated with gastroesophageal reflux disease (GERD). Additionally, a notable contrast was observed in the condition of the nasal cavity mucosa

between the anterior and posterior regions. In the anterior parts, the mucosa may exhibit no changes or demonstrate grade 1 hypertrophy based on the Camacho classification. Anterior dry rhinitis with crusts is frequently encountered.

Moving to the posterior regions of the nasal cavity, we observed severe edema, asymmetrical hypertrophy of the posterior ends of the lower nasal bones, and copious mucus production. Nasal edema was detected by two blinded raters in 75 patients (78.9%) (see Figure 1A). However, discerning these findings as a specific characteristic of chronic rhinosinusitis associated with gastroesophageal disease in adults poses a challenge.

In comparison with the control groups, this symptom was prominent in the main group, manifesting as pronounced swelling of the nasal mucosa. Conversely, reactive nasal edema was not observed in control group 1, where hypertrophic changes without active nasal edema were noted during the remission period. Control group 2 showed no alterations in the nasal mucosa, as patients in this group did not exhibit chronic rhinosinusitis or gastroesophageal reflux disease.

Significant alterations were observed in the nasopharyngeal mucosal layer. Increased vascularity of the nasopharyngeal mucosal layer was noted in 91 patients (95.7%) (refer to Figure 1B, C). The underlying pathogenetic mechanism of this vascular pattern remains unknown. However, we hypothesize that it may be caused by thinning of the mucosal layer under the influence of reflux content.

Hypertrophy of the nasopharyngeal mucosal layer was observed in 83 patients (87.4%) (see Figure 1D). In 77 patients (81.1%), mucus with varying characteristics of color and consistency was found in the nasopharynx (see Figure 1E), while no mucus or other secretions were detected in the middle nasal passages in these patients. The color of the mucus ranged from transparent to a pronounced green hue. Its consistency was viscous, characterized by thick, difficult-to-remove mucosal discharge.

Asymmetric hypertrophy of the mucosa of the oropharynx was noted in 62 patients (65.3%) (see Figure 1F). The more pronounced lesion on one side of the nose and nasopharynx was associated with a preference for falling asleep and sleeping on either the right or left side. Therefore, we propose that these hypertrophic changes in the nose and nasopharynx may be induced by the effect of acidic reflux content.

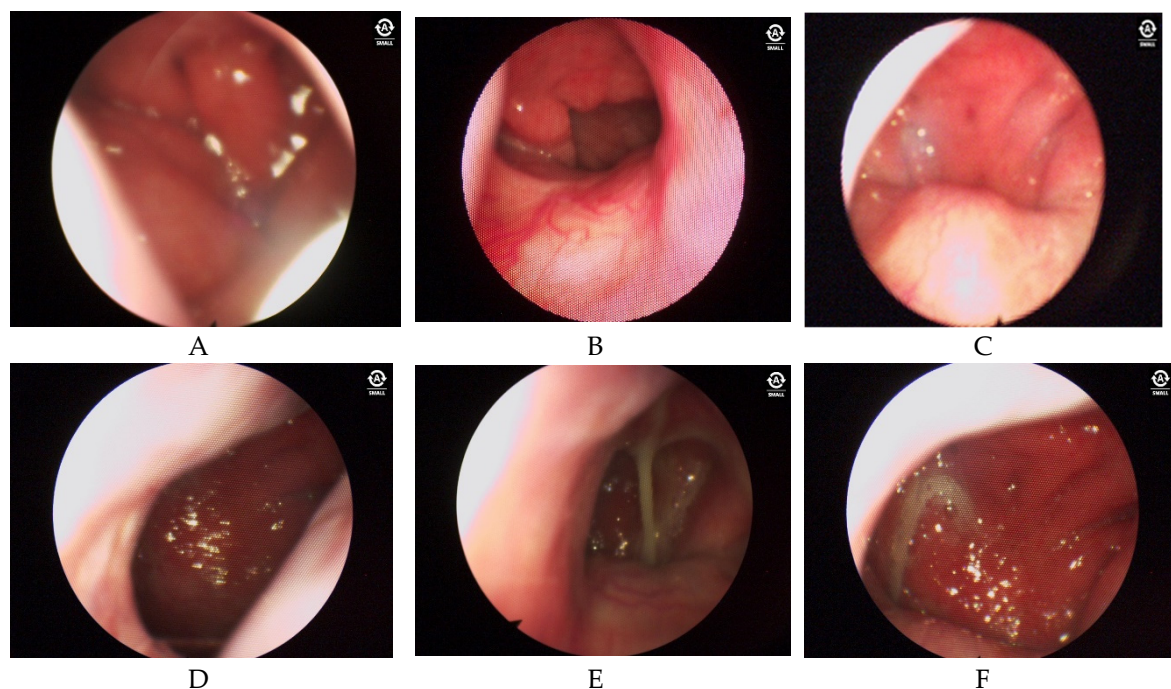


Figure 1. Endoscopic findings.

Based on the endoscopic findings described in the results, the criteria for diagnosing chronic rhinosinusitis associated with symptoms of gastroesophageal reflux disease (GERD) include:

Alterations in Nasal Cavity Mucosa:

Posterior Nasal Cavity: Presence of distinct alterations in the mucosa, particularly at the posterior end of the inferior nasal concha.

Anterior Nasal Cavity: Mucosa may show no changes or grade 1 hypertrophy according to the Camacho classification. Anterior dry rhinitis with crusts may also be observed.

Posterior Nasal Cavity: Severe edema, asymmetrical hypertrophy of the posterior ends of the lower nasal bones, and copious mucus production.

Nasal Edema:

Presence of nasal edema detected by two blinded raters in a significant percentage of patients (78.9%).

Nasopharyngeal Mucosal Alterations:

Increased Vascularity: Noted in a majority of patients (95.7%), indicating possible inflammation or irritation.

Hypertrophy: Observed in a high percentage of patients (87.4%), suggesting chronic inflammation.

Mucus Production: Present in a majority of patients (81.1%), with varying characteristics of color and consistency.

Oropharyngeal Asymmetry:

Asymmetric hypertrophy of the mucosa of the oropharynx noted in a significant percentage of patients (65.3%), potentially influenced by sleeping position preference.

These endoscopic findings, when observed in conjunction with symptoms suggestive of both chronic rhinosinusitis and GERD, contribute to the diagnosis of chronic rhinosinusitis associated with symptoms of gastroesophageal reflux disease in adults.

After analyzing all the data collected, we have concluded that in chronic rhinosinusitis associated with gastroesophageal disease, the mucosal layer of the posterior parts of the nose and nasopharynx undergoes continuous inflammatory processes due to the regular influence of acidic reflux content.

4. Discussion

Our study findings indicate that gastroesophageal reflux exerts an influence on the mucosal layer of the nasal cavity and nasopharynx, akin to its effect on the larynx and pharynx, characterized by edema, mucus presence, and increased vascularization with hyperemia and hypertrophy. Several studies have underscored the etiopathogenetic role of gastroesophageal reflux in sinus and nasopharyngeal inflammation [11–14]. Analysis of the causal relationship between GERD and chronic rhinosinusitis at the genetic level has revealed that gastroesophageal reflux disease increases the risk of developing chronic rhinosinusitis by 36% [15]. In our study, we identified specific abnormalities: significant changes in the mucosa of the posterior parts of the nose (including the posterior ends of the lower nasal turbinates and the nasopharyngeal region). Similar to findings in the pharynx [16], we also observed an increased vascular pattern and the presence of mucus in the posterior parts of the nose and nasopharynx. A study investigating the relationship between laryngopharyngeal reflux and otitis media with effusion in children demonstrated that pepsin levels gradually increased as the viscosity of the fluid in the middle ear cavity increased [12]. It is believed that exposure to gastric contents via nasopharyngeal reflux triggers hypersecretion of mucus in the nasopharynx.

The excessive production of mucus results in postnasal drip syndrome, which constitutes the primary source of discomfort for individuals with nasopharyngeal reflux, consequently diminishing their quality of life. This syndrome is typified by the drainage of nasal secretions from the nose, passing through the nasopharynx, and pooling at the posterior wall of the pharynx. Many patients often describe difficulty in clearing this viscous mucus when attempting to blow their nose or swallow.

In our study, we observed significant alterations in the nasopharyngeal and nasal mucosal layers. Various theories exist regarding how gastroesophageal reflux disease impacts the nasal and nasopharyngeal cavities. One hypothesis suggests that the acidic reflux contents may directly affect the nasal and nasopharyngeal mucosal layers, as evidenced by a reaction similar to that observed in the esophageal mucosa upon direct contact with gastric contents, including the expression of pepsin A and heat shock protein 70 [17]. Another theory implicates *Helicobacter pylori* in the development of chronic rhinosinusitis, potentially leading to the formation of nasal polyps [18]. Additionally, autonomic nervous system dysfunction associated with gastroesophageal reflux disease may contribute to the pathogenesis through an existing nerve reflex between the esophagus and the sinuses via the vagus nerve [18].

The characteristics of changes in the nasal and nasopharyngeal mucosa observed during endoscopic examination of the nose and nasopharynx in patients with nasopharyngeal reflux are presented in Table 4.

Table 4. Signs of exposure to nasopharyngeal reflux.

	Signs of exposure to nasopharyngeal reflux	0	1	Total score
nose	Asymmetry between the anterior and posterior regions of the nasal cavity			
	Predominantly unilateral hypertrophy of the posterior end of the inferior turbinate			
	Absence of mucus in the middle nasal passage			
nasopharynx	Hypertrophy of the posterior wall of the nasopharynx			
	Hypertrophy of the Eustachian junction			
	Increased vascular pattern			
	Presence of mucus			

5. Conclusions

Our comprehensive study, encompassing 95 patients with chronic rhinosinusitis accompanied by symptoms of gastroesophageal reflux disease (GERD) along with two meticulously chosen control groups, has illuminated profound alterations in the mucosal landscape of the posterior nasal and nasopharyngeal cavities. These discerning findings have not only shed light on the intricate interplay between chronic rhinosinusitis and GERD but have also furnished a practical framework for the nuanced differential diagnosis of the etiopathogenetic trajectory of chronic rhinosinusitis. By offering this pragmatic diagnostic approach, our research holds the potential to serve as a valuable tool for general practitioners and otolaryngologists, empowering them to precisely identify the underlying triggers of chronic rhinosinusitis. Through such accurate diagnoses, clinicians may be better equipped to implement tailored interventions, ultimately mitigating the frequency and severity of exacerbations in affected individuals. We posit that our study heralds a promising avenue for further exploration, advocating for continued research endeavors to deepen our understanding of this intricate relationship and optimize patient care strategies accordingly.

Author Contributions: Conceptualization, Kalamkas T. Sagandykova, Nataliya M. Papulova, and Talapbek M. Azhenov; methodology Kalamkas T. Sagandykova; software Aliya Darbekova; validation, Nataliya M. Papulova, and Talapbek M. Azhenov; investigation, Kalamkas T. Sagandykova and Nataliya M. Papulova; writing—original draft preparation, Kalamkas T. Sagandykova; writing—review and editing, Kalamkas T. Sagandykova and Jerome R. Lechien.; visualization, Kalamkas T. Sagandykova; supervision, Jerome R. Lechien; All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by Local Ethical Commission of the NpJSC “Astana Medical University” (protocol code LCB NpJSC AMU #13 date 11/29/2023).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Fokkens WJ, Viskens AS, Backer V, Conti D, De Corso E, Gevaert P, Scadding GK, Wagemann M, Bernal-Sprekelsen M, Chaker A, Heffler E, Han JK, Van Staeyen E, Hopkins C, Mullol J, Peters A, Reitsma S, Senior BA, Hellings PW. EPOS/EUFOREA update on indication and evaluation of Biologics in Chronic Rhinosinusitis with Nasal Polyps 2023. *Rhinology*. 2023 Jun 1;61(3):194-202. doi: 10.4193/Rhin22.489. PMID: 36999780..
2. Sella GCP, Tamashiro E, Anselmo-Lima WT, Valera FCP. Relation between chronic rhinosinusitis and gastroesophageal reflux in adults: systematic review. *Braz J Otorhinolaryngol*. 2017 May-Jun;83(3):356-363. doi: 10.1016/j.bjorl.2016.05.012. Epub 2016 Jul 14. PMID: 27470496; PMCID: PMC9444733.
3. Gyawali CP, Yadlapati R, Fass R, Katzka D, Pandolfino J, Savarino E, Sifrim D, Spechler S, Zerbib F, Fox MR, Bhatia S, de Bortoli N, Cho YK, Cisternas D, Chen CL, Cock C, Hani A, Remes Troche JM, Xiao Y, Vaezi MF, Roman S. Updates to the modern diagnosis of GERD: Lyon consensus 2.0. *Gut*. 2024 Jan 5;73(2):361-371. doi: 10.1136/gutjnl-2023-330616. PMID: 37734911; PMCID: PMC10846564.
4. Belafsky PC, Postma GN, Koufman JA. The validity and reliability of the reflux finding score (RFS). *Laryngoscope*. 2001 Aug;111(8):1313-7. doi: 10.1097/00005537-200108000-00001. PMID: 11568561.
5. Lechien JR, Bobin F, Muls V, Mouawad F, Dapri G, Dequanter D, Horoi M, Thill MP, Rodriguez Ruiz A, Saussez S. Changes of Laryngeal and Extralaryngeal Symptoms and Findings in Laryngopharyngeal Reflux Patients. *Laryngoscope*. 2021 Jun;131(6):1332-1342. doi: 10.1002/lary.28962. Epub 2020 Aug 5. PMID: 32757218..
6. Zeleník K, Javorská Z, Taimrová R, Vrtková A, Hránková V, Tedla M, Lukáčová K, Lubojacký J, Formánek M, Komínek P. Association Between Inferior Turbinate Hypertrophy and Extraesophageal Reflux. *JAMA Otolaryngol Head Neck Surg*. 2022 Aug 1;148(8):773-778. doi: 10.1001/jamaoto.2022.1638. PMID: 35771544; PMCID: PMC9247855.
7. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). *J Voice*. 2002 Jun;16(2):274-7. doi: 10.1016/s0892-1997(02)00097-8. PMID: 12150380.
8. Lechien JR, Bobin F, Rodriguez A, Dequanter D, Muls V, Huet K, Harmegnies B, Crevier-Buchman L, Hans S, Saussez S, Carroll TL. Development and Validation of the Short Version of the Reflux Symptom Score: Reflux Symptom Score-12. *Otolaryngol Head Neck Surg*. 2021 Jan;164(1):166-174. doi: 10.1177/0194599820941003. Epub 2020 Jul 21. PMID: 32689876.
9. Camacho M, Zaghi S, Certal V, Abdullatif J, Means C, Acevedo J, Liu S, Brietzke SE, Kushida CA, Capasso R. Inferior turbinate classification system, grades 1 to 4: development and validation study. *Laryngoscope*. 2015 Feb;125(2):296-302. doi: 10.1002/lary.24923. Epub 2014 Sep 12. PMID: 25215619.
10. Camacho M, Zaghi S, Certal V, Abdullatif J, Modi R, Sridhara S, Tolisano AM, Chang ET, Cable BB, Capasso R. Predictors of Nasal Obstruction: Quantification and Assessment Using Multiple Grading Scales. *Plast Surg Int*. 2016;2016:6945297. doi: 10.1155/2016/6945297. Epub 2016 May 16. PMID: 27293885; PMCID: PMC4884800.
11. Anzić SA, Turkalj M, Župan A, Labor M, Plavec D, Baudoin T. Eight weeks of omeprazole 20 mg significantly reduces both laryngopharyngeal reflux and comorbid chronic rhinosinusitis signs and symptoms: Randomised, double-blind, placebo-controlled trial. *Clin Otolaryngol*. 2018 Apr;43(2):496-501. doi: 10.1111/coa.13005. Epub 2017 Oct 23. PMID: 29024410.
12. Luo HN, Yang QM, Sheng Y, Wang ZH, Zhang Q, Yan J, Hou J, Zhu K, Cheng Y, Wang BT, Xu YL, Zhang XH, Ren XY, Xu M. Role of pepsin and pepsinogen: linking laryngopharyngeal reflux with otitis media with effusion in children. *Laryngoscope*. 2014 Jul;124(7):E294-300. doi: 10.1002/lary.24538. Epub 2014 Jan 15. PMID: 24284944.
13. Brunworth JD, Mahboubi H, Garg R, Johnson B, Brandon B, Djalilian HR. Nasopharyngeal acid reflux and Eustachian tube dysfunction in adults. *Ann Otol Rhinol Laryngol*. 2014 Jun;123(6):415-9. doi: 10.1177/0003489414526689. PMID: 24671547.
14. Brar S, Watters C, Watson N, Birchall M, Karagama Y. Ear, nose and throat (ENT) manifestations and complications of reflux. *Frontline Gastroenterol*. 2022 Jun 7;13(e1):e57-e64. doi: 10.1136/flgastro-2022-102184. PMID: 35812029; PMCID: PMC9234721.
15. Chen G, Guo W, Liu S, Wang Y, Zhang X. Causal analysis between gastroesophageal reflux disease and chronic rhinosinusitis. *Eur Arch Otorhinolaryngol*. 2024 Apr;281(4):1819-1825. doi: 10.1007/s00405-023-08350-w. Epub 2024 Jan 8. PMID: 38189968.
16. Lechien JR, Rodriguez Ruiz A, Dequanter D, Bobin F, Mouawad F, Muls V, Huet K, Harmegnies B, Remacle S, Finck C, Saussez S. Validity and Reliability of the Reflux Sign Assessment. *Ann Otol Rhinol Laryngol*. 2020 Apr;129(4):313-325. doi: 10.1177/0003489419888947. Epub 2019 Nov 15. PMID: 31729247.

17. Ren JJ, Zhao Y, Wang J, Ren X, Xu Y, Tang W, He Z. PepsinA as a Marker of Laryngopharyngeal Reflux Detected in Chronic Rhinosinusitis Patients. *Otolaryngol Head Neck Surg.* 2017 May;156(5):893-900. doi: 10.1177/0194599817697055. PMID: 28457223.
18. Chen WC, Chang YT, Chen SF, Lin WC, Su YY, Luo SD. The symptom burden of autonomic dysfunction is positively associated with chronic rhinosinusitis status. *Rhinology.* 2018 Sep 1;56(3):227-233. doi: 10.4193/Rhin18.005. PMID: 29561920.

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.