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Association Between Helicobacter Pylori, Reflux and Chronic Rhinosinusitis: A Systematic Review.

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Abstract:	Background: The prevalence, role, and clinical relevance of Helicobacter Pylori (HP) in sinonasal tissues of patients with chronic rhinosinusitis remain unclear. Objective: To investigate the prevalence and clinical relevance of Helicobacter Pylori (HP) in chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP) and without nasal polyps (CRSSNP). Methods: Three investigators conducted a PubMed, Scopus, and Cochrane Library
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Association Between Helicobacter Pylori, Reflux and Chronic Rhinosinusitis: A Systematic Review.

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Association Between Helicobacter Pylori, Reflux and Chronic Rhinosinusitis: A Systematic Review.

Abstract

Background: The prevalence, role, and clinical relevance of Helicobacter Pylori (HP) in sinonasal tissues of patients with chronic rhinosinusitis remain unclear.

Objective: To investigate the prevalence and clinical relevance of Helicobacter Pylori (HP) in chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP) and without nasal polyps (CRSSNP).

Methods: Three investigators conducted a PubMed, Scopus, and Cochrane Library systematic review of the prevalence and clinical relevance of HP infection in CRS patients through the PRISMA framework. A bias analysis was conducted to identify potential heterogeneity and biases across studies.

Results: Of the 42 identified studies, 20 met the inclusion criteria, accounting for 741 CRS patients and 368 controls. HP was detected in 37.1% (n=127/342) of polyps of CRSwNP patients with the polymerase chain reaction (PCR) and 32.7% (n=37/113) of polyp tissue with the immunohistochemistry (IHC). Controls reported a nasal PCR and IHC detection rates of 14.8% (n=36/243) and 3.6% (n=3/84), respectively. The HP rate did not differ between CRSwNP and CRSsNP. Among patients with CRS, the enzyme-linked immunosorbent assay testing detected blood HP antigens in 48.7% (n=74/152) of CRS patients and 41.6% (n=37/89) of controls. The detection of HP in polyps was associated with the severity of gastroesophageal reflux disease (GERD). There was an important heterogeneity between studies for the inclusion criteria, methods of HP detection, and reflux outcomes.

Conclusion: Helicobacter Pylori can be detected in one-third of sinonasal tissues from patients with CRS and can be considered a biomarker of GERD. The potential role of HP in the

development of CRS remains unclear. The heterogeneity between studies limits the drawing of valid conclusions.

Keywords: Chronic Rhinosinusitis; Otolaryngology; Otorhinolaryngology; Laryngopharyngeal; Gastroesophageal; Reflux; Helicobacter Pylori; Polyp.

Introduction

Chronic rhinosinusitis (CRS) represents a significant health issue, ranking as one of the most prevalent chronic disorders in the U.S. and Europe.[1] CRS can be classified into CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSSNP), each with distinct physiological and pathological features.[2] The etiology of CRS is multifactorial, with several contributing factors, including viral infections, asthma, allergies, immune deficiencies, and environmental exposures such as smoking and pollution.[3,4] Laryngopharyngeal reflux disease (LPRD) has long been identified as a contributing factor of CRS through the deposit of gastroduodenal enzymes in the nasal mucosa, leading to inflammation and meatus obstruction.[5] The refluxate gastroduodenal content in the otolaryngological region may include the common gastroduodenal enzymes (e.g., pepsin bile salts, elastase), cholesterol, and Helicobacter pylori (HP).[6,7] Then, H. *pylori* (HP) is suspected to be associated with the development and the severity of several otorhinolaryngological conditions, including chronic tonsillitis, chronic otitis media, or LPRD.[8-10] In addition to its potential pathophysiological role, HP could be an indirect biomarker of LPRD.

The objective of this systematic review was to explore the prevalence and clinical relevance of HP in CRS.

Materials and Methods

The criteria for study inclusion were based on the population, intervention, comparison, outcome, timing, and setting (PICOTS) framework.[11] Three authors independently reviewed and extracted data according to the PRISMA checklist for systematic reviews and the EQUATOR network reporting guidelines.[12]

Type of studies: The authors included uncontrolled, controlled prospective, or retrospective studies investigating the presence of HP in adult patients with CRSwNP or CRSSNP. The studies had to be published between January 1990 and September 2024 in English, Spanish, or French peer-reviewed journals. Case reports were excluded.

Population: The diagnosis of CRS was based on the clinical criteria defined by the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS),[2] involving the evaluation of symptoms, findings, sinus CT-scan, and histological examination (polyps). The study included operated CRS patients or individuals with unoperated CRS and histopathological samples. In patients undergoing functional endoscopic sinus surgery (FESS), the presence of HP was identified in either sinonasal secretions or mucosa samples. In the selected studies, various methods were used for the diagnosis of HP, including enzyme-linked immunosorbent assay (ELISA), polymerase chain reaction (PCR), gastric biopsy, urease tests (such as the Campilobacter-like organism (CLO) test and CLO broth test), C-urea breath test, modified McMullen test, Giemsa stain, hematoxylin and eosin (H&E) stain, culture, stool antigen test, and immunohistochemistry (IHC).

Among studies investigating reflux diseases, the authors considered the diagnosis of Gastroesophageal reflux disease (GERD) according to the Lyon consensus.[13] GERD consists of grade C or D esophagitis (Los Angeles grading), esophageal stricture, or acid exposure time >6% of the testing time.[13] The LPRD diagnosis was based on Dubai consensus,[13] which suggests the confirmation of the diagnosis for patients with more than one pharyngeal reflux event at the 24-hour multichannel intraluminal impedance-pH monitoring (HEMII-pH).

Intervention and comparison: The study included untreated patients or patients undergoing FESS. For controlled studies, the analysis should primarily compare the presence of HP in patients with CRS *versus* healthy individuals (controls).

Outcomes: The following outcomes were reviewed: study design, number of patients, gender ratio, mean age, HP detection, CRS and reflux diagnosis, CRS types, and outcomes. Blood, mucosa, and air detection of HP were considered.

Timing and setting: There were no criteria for specific stages or timing in the 'disease process' of the study population.

Research strategy

The publication search was conducted on PubMed, Embase, and Cochrane Library by three independent investigators (JRL, JK, KR). The database was screened for abstracts and titles referring to the description of data related to the investigation of HP in CRS patients. The findings of the search strategy were reviewed for relevance, and the reference lists of these publications were examined for additional pertinent studies. The following keywords were used in the database with the Boolean operators AND/OR: 'chronic', 'rhinosinusitis', 'Helicobacter pylori', 'nasal polyps', 'reflux', 'gastroesophageal', 'laryngeal', 'laryngopharyngeal', 'pepsin' and 'PCR'. The three investigators analyzed the full texts of the selected publications. The studies were classified according to the Oxford levels of evidence (I-V) and categorized based on their design (prospective or retrospective). Additionally, the authors investigated findings from studies examining the effect of gastroduodenal reflux content on the nasal mucosa. The systematic review was not registered in PROSPERO.

Bias analysis:

The bias analysis was carried out by two investigators with the Methodological Index for Non-Randomized Studies (MINORS) tool, which is a validated instrument designed for assessing the quality of non-randomized surgical studies.[15] The MINORS tool consists of 12 items related to the analysis of methodological points of comparative and non-comparative studies. The aim

of the study was assessed as clearly stated (2), unclear (1), or absent (0). The inclusion of patients was judged for clearly reported consecutive inclusion (2), unclear consecutive inclusion (1), or no consecutive inclusion (0). The prospective data collection was evaluated as prospective (2), retrospective analysis of prospective recruited patients (1), or absent (0). The quality of endpoints was considered as high (2) if the authors assessed the outcomes with at least two validated and objective approaches on tissues (ELISA, PCR, Western blot). The use of one method was judged as moderate (1), whereas the HP indirect assessment (only blood biology or breath test) was judged fair (0). For prospective studies investigating treatments, the follow-up period was considered adequate (2) for at least 3 months of HP/reflux treatment. A shorter follow-up was considered less reliable to evaluate accurately the therapeutic effectiveness on HP outcomes. Finally, the 5% rate of patients lost to follow-up patients was considered as the threshold in the MINORS, while the study size calculation needed to be performed (2), mentioned as unnecessary (1), or absent (0). The control group was judged as valid for nasal biopsies from healthy individuals, individuals with traumatic nasal conditions, or concha bullosa without infection. Nasal conditions associated with potential infection or reflux, such as inferior turbinate hypertrophy related to gaseous reflux, or infected concha bullosa, were considered moderately valid (1). The ideal MINORS score was 16 for non-comparative studies and 24 for comparative studies.[15]

Results

Of the 42 studies initially identified, 20 met the inclusion criteria for this systematic review (Figure 1, Table 1).[15-33] There were 17 controlled[15-26,29,31-33] and 3 uncontrolled prospective studies,[27,28,30] accounting for 741 CRS patients and 368 controls (Table 1). In studies reporting gender information, there were 172 females and 339 males with CRS, respectively. The mean age was 52 years, ranging from 22 to 61 years (Table 1). Most studies (n=15) focused on the

relationship between HP and CRSwNP (Table 1).[16,19-26,28-33] The type of CRS was unspecified in one study.[18] The diagnosis of CRS was mostly based on symptoms, nasofibroscopy findings, and CT scans (Table 1). Among recent studies, the EPOS criteria have been considered in only one study.[27]

Helicobacter Pylori Detection in Chronic Rhinosinusitis

The methods used for detecting HP in nasal tissues, stomach, or blood are reported in Table 2. Most studies based the HP detection on PCR, urease, or IHC. The polymerase chain reaction (PCR) was used to document HP in 8 studies, including CRSwNP,[20-22,24,25,28,31,33] and 2 studies investigating CRSsNP patients.[15,17] Among studies using nasal PCR, HP was detected in 37.1% (n=127/342) of polyps of CRSwNP patients. The analysis of nasal tissue of controls (patients without CRSwNP or CRSsNP) reported a nasal HP PCR detection rate of 14.8% (n=36/243). IHC was used in 5 studies for detecting HP in sinonasal tissues.[16,18,19,23,26] The IHC approach revealed HP in nasal polyps in 32.7% (n=37/113) of CRSwNP patients and 3.6% (n=3/84) of controls, respectively. Regardless of the detection method, HP was found in 8.7% to 33% of patients with CRSsNP. As found in Table 1, the prevalence of HP did not differ between CRSwNP and CRSsNP patients. Among patients with CRS, the ELISA testing detected blood HP antigens in 48.7% (n=74/152) of CRS patients and 41.6% (n=37/89) of controls (Table 1).[16,24,31]

Reflux Diagnosis Criteria

GERD and LPRD were investigated in 6 studies,[15,16,26-29] and one study,[17] respectively. No GERD studies adhered to international consensus for the definition of GERD. Zika *et al*. observed that all patients with recalcitrant CRSwNP had GERD symptoms,[28] while 28 (77.8%) had gastric HP. In another investigation,[27] the severity of GERD symptoms was similarly

associated with the recurrence of CRSSNP symptoms. In the study of Bansal *et al*., 7/35 CRSwNP and 6/35 controls reported GERD symptoms, which demonstrated the lack of significant differences across groups.[26] The preliminary study of Ozdek *et al*. observed that 5/12 CRSwNP patients had GERD symptoms with 3/5 with HP detection in polyps.[15] Among the HP+ group, only one patient did not have GERD symptoms. Similarly, Cvorovic *et al*., reported that 8/23 CRSwNP patients had GERD symptoms, and among them, 6/8 had HP in nasal polyps. The authors of these two studies suggested that HP was exclusively detected in polyps of patients with both CRSwNP and GERD.[29] Dinis *et al*. investigated the pepsin and pepsinogen in sinonasal tissues of recalcitrant CRSSNP patients and controls without observing significant differences between groups.[17]

Bias Analysis

The MINORS are reported in Table 3. The inclusion and exclusion criteria used for determining the bias analysis are summarized in Appendix 1. The mean MINORS was 12.2 (standard deviation: 2.3). No study reached the adequate MINORS score. The aim of the study was clearly stated in all publications. No author reported having included consecutive patients. The collection of data was prospective in all studies. Nine teams have considered using more than one method for detecting HP,[16,17,19,22,24,28,29,31,33] and others using one method (Table 3). Al Kholy *et al*. only used a breath test, which was not associated with the detection of HP in nasal tissue.[30] The follow-up period was only evaluated in one study, where authors evaluated the effectiveness of treatment on nasal outcomes.[27] The study size calculation was not evaluated in studies. Ten studies considered patients with concha bullosa, nasal fracture, or no nasal disorders for the control group (Appendix 1; Tables).[15-17,19,21,22,24,25,26,31] The control group was judged as potentially biased in studies considering patients with nasal obstruction/inferior turbinate hypertrophy as healthy individuals regarding the potential role of LPRD in the

development of inferior turbinate hypertrophy. Five studies failed to demonstrate baseline group equivalence,[20,22,24,25,26] which was related to differences between groups for gender ratio, comorbidities, or addiction. Statistics were commonly adequate, although a lack of study size calculation in all studies.

Discussion

Since the first study detecting HP in CRSwNP in 2003,[15] the number of studies investigating the potential association between reflux, HP, and CRS has steadily increased. To date, three hypotheses have been proposed in the literature.[34,35] The first hypothesis suggests that the nasal cavity can be a passive reservoir of HP without association with gastric content and the development of CRS. The second hypothesis proposed that HP may originate from the oral cavity and reach the sinonasal region through oronasal reflux processes. The third hypothesis suggests that the stomach remains the primary reservoir of HP, and the HP can reach the sinonasal region through the backflow of gastric content into the upper aerodigestive tract (GERD and LPRD).

The findings of this systematic review of the literature support a substantially higher prevalence of nasal HP in patients with CRSwNP and CRSsNP (32.7% to 37.1%) compared to controls (3.6% to 14.8%). According to studies, the prevalence of nasal HP is comparable between CRSwNP and CRSsNP, which can suggest that HP is not necessarily associated with the development of polyps. Interestingly, two teams reported a strong and positive association between the severity of GERD symptoms and the presence of HP in CRS.[15,29] These observations were, however, mitigated by Dinis *et al.*[17] who observed a higher rate of nasal HP in CRSwNP (40%) compared to controls (20%) but no significant differences for the nasal measurements of pepsin and pepsinogen. The observations of Dinis *et al.*[17] can appear as controversial regarding the other studies,[15,29] but numerous factors can limit the drawing of

valid conclusions. On the one hand, this study included a low number of patients (n=15) and controls (n=5), which was highlighted in the MINORS assessment (13/20). On the other hand, the authors did not investigate GERD findings and partly focused on LPRD with the measurement of pepsin and pepsinogen. The consideration of pepsin and pepsinogen for the LPRD diagnosis can be biased because many patients with a demonstrated LPRD at the 24-hour HEMII-pH have no detectable pepsin in the upper aerodigestive tract.[36,37] In that way, a recent study demonstrated that several gastroduodenal enzymes and biomarkers can be refluxed in the upper aerodigestive during the reflux events, including elastase, bile acids, trypsin, all of them having a potential role in the development of the mucosa inflammation.[7,38,39] Therefore, the lack of detection of pepsin or pepsinogen in nasal tissue cannot exclude the presence of a reflux disease.[13]

In most studies investigating the role of reflux in the development of upper aerodigestive tract disorders, i.e., benign lesion of the vocal cords, chronic rhinosinusitis, and otitis media, the consideration of GERD instead of LPRD was considered as the primary limitation of studies.[5,40,41] In the case of HP in sinonasal tissue, the consideration of GERD and less LPRD makes sense regarding their different pathophysiological mechanisms and the weight of enzymes and bacteria. Indeed, GERD is a liquid disease with backflow of the stomach into the esophagus or, in some cases of severe reflux events, into the upper aerodigestive tract,[42] while LPRD primarily involves gaseous pharyngeal reflux events.[43] The weight of HP is ~10^{-12} grams (10^{12} Da), which is significantly heavier than the molecular weight of pepsin and pepsinogen (~35 kDa to 50 kDa), and bile acids (~400-600 Da). Considering that a gaseous reflux event can transport molecules with a maximum weight of ~10,000-20,000 Da, it should be difficult for HP to reach the upper aerodigestive tract through a gaseous reflux event.[44] These theoretical and physiological considerations support that the detection of HP in sinonasal tissue can highlight the presence of severe GERD rather than LPRD typical reflux events (gaseous). This

point strengthens the studies demonstrating the role of severe GERD in the development of CRS.[45,46] The future studies investigating the association between reflux diseases, HP, and CRS need to consider the study of reflux events (nature, pH, duration) through the 24-hour HEMII-pH, and the identification of all gastroduodenal enzymes (e.g., pepsin, trypsin, lipase, elastase, bile acids) in the sinonasal tissue of patients with CRS and HP.

The heterogeneity between studies in inclusion, exclusion criteria, and outcomes and the low number of patients and controls are the primary limitations of this review. In inclusion criteria, most studies focused on recalcitrant CRSwNP (Appendix1) but a few investigated patients with an untreated CRSwNP,[19,26] which can bias the comparison between studies. Moreover, some teams did not exclude patients with confounding factors, e.g. recent use of antibiotics, allergic rhinitis, antacids, and tobacco-alcohol consumption, that can bias the reflux/HP investigations. The consideration of patients with nasal obstruction requiring septoplasty and inferior turbinoplasty as controls is an additional limitation because reflux has been identified as a causal factor of posterior nasal turbinate hypertrophy (Mulberry turbinate).[47,48] Finally, the heterogeneity across studies in the method used to detect HP can influence some results outcomes, which limited the comparison between studies.

Conclusion

Helicobacter Pylori can be detected in one-third of sinonasal tissues from patients with CRS and can be considered a biomarker of GERD. The potential role of HP in the development of CRS remains unclear. The heterogeneity between studies in inclusion criteria, methods of HP detection, and reflux outcomes limit the drawing of valid conclusions.

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Table 1: Demographics and Clinical Features of Studies.

References	Design	EL	N	F/M	Age	Reflux Criteria	CRS Criteria	HP Detection	HP sinonasal Outcomes
Özdek, 2003 (15)	Pros. Contr.	IIB	12 CRSSNP	5/7	36	GERD	Symptoms & CT	PCR (nasal)	CRS: 4/12
			13 HC	8/5	36	symptoms			HC: 0/13
Koc, 2004 (16)	Pros. Contr.	IIB	30 CRSwNP	13/17	42	GERD	Symptoms, CT	ELISA (blood)	CRS/HC: 26/30-17/20
			20 HC	9/11	40	symptoms	Histology	IHC (nasal)	CRS/HC: 6/30-0/20
Dinis, 2006 (17)	Pros. Contr.	IIB	15 rCRSSNP	4/11	50	Nasal pepsin &	Recalcitrant	ureA PCR (nasal)	CRS/HC: 6/15-1/5
			5 HC	4/1	38	pepsinogen	symptoms & CT	Pepsin	CRS=HC
Kim, 2007 (18)	Pros. Contr.	IIB	48 rCRS	17/31	42	NP	Symptoms & CT	CLO IHC (nasal)	CRS: 12/48
			29 HC	17/12	38				HC: 1/29
Özcan, 2008 (19)	Pros. Contr.	IIB	25 CRSwNP	9/16	37	NP	Symptoms, CT,	IHC (nasal)	CRS/HC: 0/25-0/14
			14 HC	4/10	31		Endoscopy	CLO	CRS/HS: 1/25-2/14
								ELISA (blood)	CRS/HC: 7/25-3/14
Cvorovic, 2008 (29)	Pros. Contr.	IIB	23 CRSwNP	11/12	43.0	GERD	Symptoms, CT,	Gastric Giemsa HP	CRS/HC: 10/23-0/15
			15 HC	7/8	37.0	Symptoms	Endoscopy	CLO (nasal)	CRS/HC: 6/23-0/15
								GERD	CRS/HC: 8/23-1/15
Ozyurt, 2009 (20)	Pros. Contr.	IIB	33 CRSwNP	5/28	34	NP	Symptoms, CT,	PCR (nasal)	CRS: 19/32
			29 HC	0/27	22		Endoscopy	ureC/cagA	HC: 19/27
Burduk, 2011 (21)	Pros. Contr.	IIB	20 CRSwNP	7/13	48.7	Symptoms	Symptoms, CT,	nasal ureA &	CRS/HC: 20/20-10/10
			10 HC	4/6	43.3	Signs of	Endoscopy	cagA PCRs	CRS/HC: 0/20-0/10
			30 Larynx	18/12	49.0	benign diseases		Larynx PCR	Larynx: 30-7/30
Nemati, 2011 (22)	Pros. Contr.	IIB	25 CRSwNP	9/15	32.1	NP	Symptoms & CT	ureC CLO	CRS/HC: 0/25-0/25
			25 HC	15/9	24.4		Endoscopy	PCR (nasal)	
Jelavic, 2012 (23)	Pros. Contr.	IIB	28 CRSwNP HP+	7/21	52	NP	Symptoms & CT	IHC (nasal)	Postop improvement:
			12 CRSwNP HP-	5/7	43		Endoscopy		HP+ > HP-
Včeva, 2012 (24)	Pros. Contr.	IIB	35 CRSwNP	10/25	54.0	NP	Symptoms & CT	PCR (nasal)	CRS/HC: 10/35-0/30
			30 HC	18/12	42.5		Endoscopy	ELISA	CRS/HC: 30/35-16/30

Alkholy, 2012 (30)	Pros. Uncontr.	IV	40 CRSwNP 104 CRSSNP	NP	29.5	NP	NP	Breath test	CRSwNP: 5/40 CRSSNP: 9/104
Kadhemi, 2012 (33)	Pros. Contr.	IIB	37 CRSwNP 38 HC	NP	NP	NP	Symptoms, CT, Endoscopy	PCR (nasal) Urease	CRS-HC: 27/37-12/38 CRS-HC: 9/37-0/38
Nikakhlagh, 2014 (25)	Pros. Contr.	IIB	50 rCRSwNP 50 HC	5/45 24/25	40.0 30.0	NP	Symptoms & CT	PCR (nasal)	CRS: 9/50 HC: 2/50
Bansal, 2016 (26)	Pros. Contr.	IIB	35 CRSwNP 35 HC	15/20 3/32	32.0 28.2	GERD symptoms	Symptoms & CT	IHC (nasal)	CRS: 14/35 HC: 3/35
Shokrollahi, 2016 (31)	Pros. Contr.	IIB	51 CRSwNP* 25 HC	NP	37.5 31.0	NP	Symptoms, CT, Endoscopy	PCR (nasal) ELISA (blood)	CRS/HC:20/62-1/25 CRS/HC: 9/62-1/25
Siupsinskiene, 2018 (32)	Pros. Contr.	IIB	45 rCRSwNP 30 HC	19/29 6/24	51.8 41.6	NP	Symptoms, CT, Endoscopy	PCR (nasal)	CRS/HC: 13/45-1/30
Lechien, 2021 (27)	Pros. Uncontr.	IV	37 CRSSNP	20/17	43.5	GERD symptoms	EPOS	Gastric HP PCR culture	CRS: 9/37
Zika, 2023 (28)	Pros. Uncontr.	IV	36 rCRSwNP	11/25	61.0	GERD Symptoms	Symptoms & CT	Gastric HP PCR (nasal) CLO (nasal) GERD	CRS: 28/36 CRS: 9/36 CRS: 11/36 36/36

Table 1 footnotes: Abbreviations: CLO= Campylobacter-Like Organism; CT=computed tomography; CRSSNP=chronic rhinosinusitis without nasal polyps; (r) CRSwNP=(recalcitrant) chronic rhinosinusitis with nasal polyps; ELISA= enzyme-linked immunosorbent assay; GERD=gastroesophageal reflux disease; HC=healthy control; HP=Helicobacter Pylori; IHC= immunochemistry; NP=not provided; PCR=polymerase reaction chain.

Table 2 : Methods for Dectecting HP.

HP diagnostic tools	N	references
Sinonasal PCR	11	15,17,20,21,22,24,25,28,31-33
Nasal urease test (CLO)	7	18,19,22,26,28,29,33
Sinonasal IHC	5	16,18,19,23,26
ELISA	4	16,19,24,31
Gastric Giemsa (PCR)	3	27-29
stool antigen test	1	26
Breath test	1	30

Table 2 footnotes : Abbreviations: ELISA= enzyme-linked immunosorbent assay; HP=Helicobacter Pylori; IHC=immunochemistery; PCR=polymerase reaction chain.

Figure 1: Flow chart

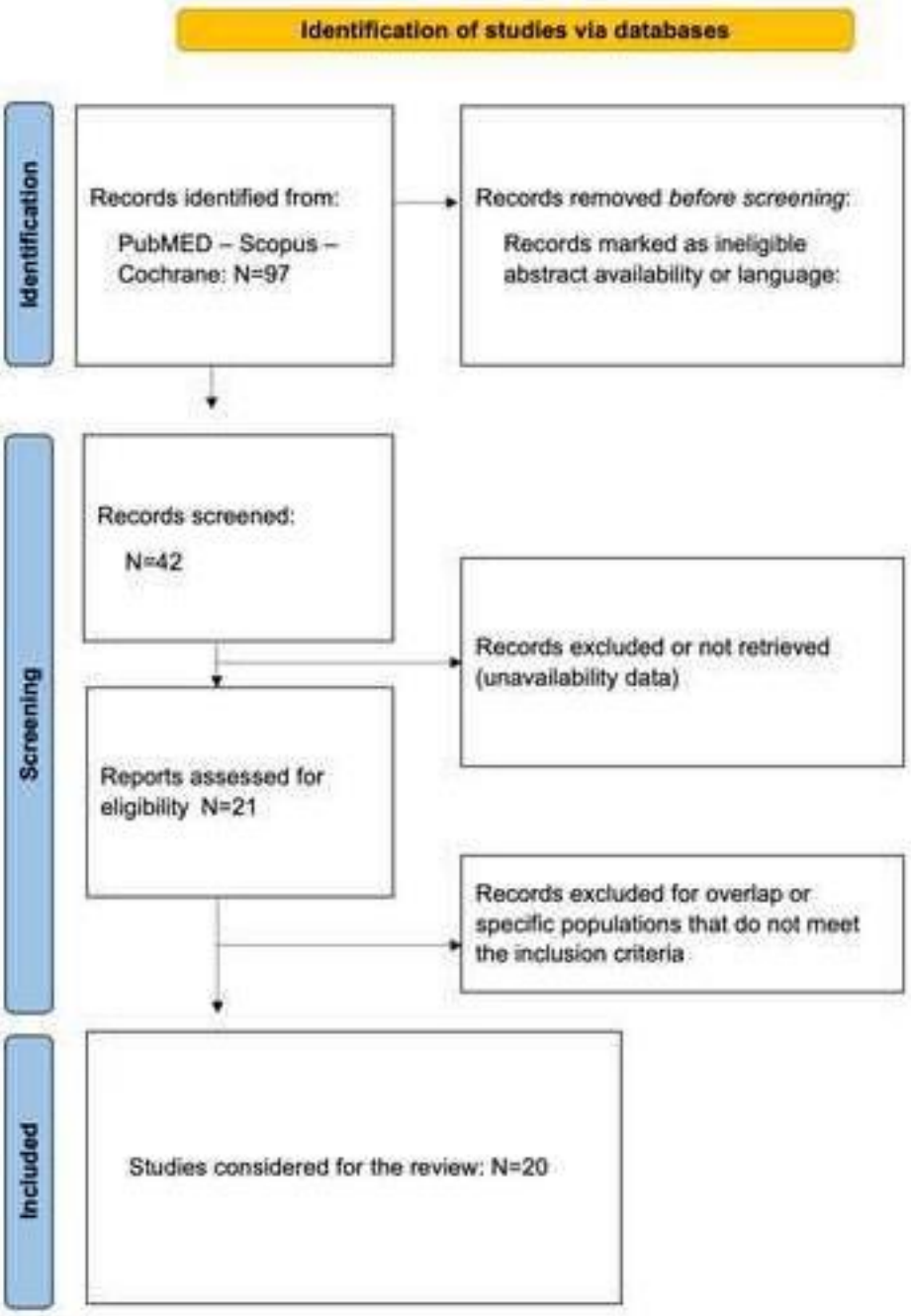
Figure 1 footnotes: -.

Table 3: MINORS.

References	Clearly Stated Aim	Conse-cutive patients	Prospective data collection	Endpoints appropriate to study	Unbiased endpoint assessment	Follow-up adequate period	<5% lost of follow-up	Study size population calculation	Adequate Control Group	Contem-porary groups	Baseline Group Equivalence	Adequate Stat Analyses	Total MINORS score
Özdek, 2003 (15)	2	0	2	1	1	-	-	0	2	2	1	1	12
Koc, 2004 (16)	2	0	2	2	2	-	-	0	2	2	1	2	15
Dinis, 2006 (17)	2	0	2	2	1	-	-	0	2	2	1	1	13
Kim, 2007 (18)	2	0	2	1	2	-	-	0	1	2	2	2	14
Özcan, 2008 (19)	2	0	2	2	2	-	-	0	2	2	1	1	14
Cvorovic, 2008 (29)	2	0	2	2	2	-	-	0	1	2	1	1	13
Ozyurt, 2009 (20)	2	0	2	1	2	-	-	0	1	2	0	2	12
Burduk, 2011 (21)	2	0	2	1	2	-	-	0	2	2	1	1	13
Nemati, 2011 (22)	2	0	2	2	2	-	-	0	2	2	0	2	14
Jelavic, 2012 (23)	2	0	2	1	2	-	-	0	-	-	-	2	9
Včeva, 2012 (24)	2	0	2	2	2	-	-	0	2	2	0	2	14
Alkholy, 2012 (30)	2	0	2	0	0	-	-	0	-	-	-	2	6
Kadhemi, 2012 (33)	2	0	2	2	0	-	-	0	1	2	1	2	12
Nikakhlagh, 2014 (25)	2	0	2	1	2	-	-	0	2	2	0	2	13
Bansal, 2016 (26)	2	0	2	1	1	-	-	0	2	2	0	2	12
Shokrollahi, 2016 (31)	2	0	2	2	2	-	-	0	2	2	1	2	15
Siupsinskiene, 2018 (32)	2	0	2	1	1	-	-	0	1	2	1	2	12
Lechien, 2021 (27)	2	0	2	1	2	2	-	0	-	-	-	2	11
Zika, 2023 (28)	2	0	2	2	1	-	-	0	-	-	-	1	8

Table 3 footnotes: Abbreviations: MINORS= Methodological Index for Non-Randomized Studies.

Figure 1



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Article

Endoscopic Features of Chronic Rhinosinusitis in Patients with Gastroesophageal Reflux Disease

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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*: Chronic rhinosinusitis is a multifactorial disease with various underlying etiologies, including inflammation, anatomical factors, and environmental triggers. While gastroesophageal reflux disease has been suggested as a potential contributor to chronic rhinosinusitis, 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 gastroesophageal reflux disease 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 gastroesophageal reflux disease 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

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1. Introduction

Adult chronic rhinosinusitis (CRS) is an inflammation of the mucosal layer of the nose and paranasal sinuses, characterized by two or more symptoms, one of which must be

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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. The 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 computed tomography (CT) changes such as mucosal changes in the osteomeatal complex and/or sinuses [1]. Chronic rhinosinusitis significantly impacts the quality of life and healthcare systems, with an estimated prevalence of 10–12% in the general population [1].

Classification According to European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS): Endotypes and Phenotypes. According to the EPOS, chronic rhinosinusitis with nasal polyps (CRSwNP) can be further classified into different endotypes based on underlying pathophysiological mechanisms, which include type 2 inflammation (eosinophilic) and non-type 2 inflammation (neutrophilic). The type 2 endotype is characterized by eosinophilic inflammation and elevated levels of interleukins IL-4, IL-5, and IL-13, whereas non-type 2 endotypes are less well defined and may involve neutrophilic inflammation. The pathophysiology of CRSwNP involves a complex interplay of genetic, environmental, and immunological factors leading to chronic inflammation. Epidemiological studies indicate that chronic rhinosinusitis with nasal polyps affects about 2–4% of the general population.

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 [1]. 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 gastroesophageal reflux disease treatment or long-term medical therapy [2]. Changes in the laryngeal mucosal layer due to laryngopharyngeal reflux were first described and systematized in 2001 by Belafsky et al. [3]. 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 [4]. In 2022, Zeleník et al. identified a relationship between hypertrophy of the inferior turbinate and extraesophageal reflux [5].

Treatment for chronic rhinosinusitis with nasal polyps typically includes a combination of medical and surgical approaches. Initial management often involves intranasal corticosteroids to reduce inflammation and polyp size [1,6]. Endoscopic sinus surgery (ESS) is considered for patients who do not respond to medical therapy, aiming to restore sinus ventilation and drainage [1,7].

Novel Therapeutics for chronic rhinosinusitis with nasal polyps. Recent advances in the understanding of the immunopathology of CRSwNP have led to the development of novel biologic therapies targeting specific inflammatory pathways. Biologics such as dupilumab (anti-IL-4Rα), mepolizumab (anti-IL-5), and omalizumab (anti-IgE) have shown promise in clinical trials, offering new hope for patients with refractory chronic rhinosinusitis with nasal polyps [8,9]. These therapies work by modulating the immune response, thereby reducing the polyp burden and improving symptoms and quality of life.

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 gastroesophageal reflux disease and chronic rhinosinusitis.

The aim of our study is to 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 expect this study to contribute to improved care for patients with chronic rhinosinusitis by facilitating more accurate diagnostic and therapeutic strategies.

We hypothesize that patients with chronic rhinosinusitis and concomitant gastroesophageal acid reflux disease will exhibit distinct endoscopic features compared with those without reflux symptoms, indicating a potential link between gastroesophageal reflux and the exacerbation or persistence of chronic rhinosinusitis.

2. Materials and Methods

The Local Ethical Commission of "Astana Medical University" NpJSC approved the study protocol (LCB NpJSC AMU #13). The database is available as 10.6084/m9.figshare.25594425.

2.1. Study Design and Population

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. The diagnosis was confirmed through computed tomography and endoscopic imaging.

All patients were examined using endoscopic diagnostic methods during the remission period, outside of exacerbations of chronic rhinosinusitis, and before starting anti-reflux treatment for gastroesophageal reflux disease. All patients underwent a clinical evaluation by a gastroenterologist, which included esophagogastroduodenoscopy and pH measurement of the esophagus.

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, had a history of laryngeal cancer, or were pregnant were excluded from the study, resulting in a final group of 95 patients. The study included patients with no history of smoking for the last 5 years or more. During the study, two patients with suspected malignant tumors of the larynx were referred for consultation to an oncologist and were excluded from the study. Active seasonal allergies or asthma were determined based on the medical history. The medical history included data from an allergist's examination, which comprised spirometry and skin tests.

The control group 1 included 41 patients with chronic rhinosinusitis but without GERD symptoms. The control group 2 consisted of 10 patients who showed no signs of chronic rhinosinusitis or GERD symptoms.

2.2. CRS Characteristics

- Total Cohort (91 + 41 patients):

The clinical symptoms were as follows: nasal congestion (94.69%), nasal discharge (anterior or posterior) (56.81%), facial pain/pressure (36.36%), decreased or lost sense of smell (46.21%), and general discomfort (18.93%).

Classification was as follows: type 2 (eosinophilic), 34.1% vs. non-type 2 (neutrophilic), 65.9%; CRSwNP, 44.7% vs. CRSsNP, 55.3%.

Comorbidities were as follows: chronic otitis media, 26.51%; allergic rhinitis, 25.75%; asthma, 19.69%; nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (NERD), 12.87%; and sleep disturbances, including obstructive sleep apnea (OSA), 5.3%.

The treatment history was as follows: one or more operations on the sinuses, 75.51%; antibacterial treatment with a course of more than 10 days, more than three times a year, in the last 5 years, 58.33%. All patients had been treated repeatedly for more than 1 month with topical corticosteroids.

The CT and endoscopic findings in our study correlated well with each other, providing additional information that improved the diagnostic accuracy and facilitated treatment planning.

- Mucosal Thickening:

The CT findings were as follows: CT scans revealed mucosal thickening of the sinuses, a common feature of CRS.

The endoscopic findings were as follows: endoscopy revealed swollen and inflamed mucosa consistent with areas of mucosal thickening seen on CT scans.

- Nasal Polyps:

The CT findings were as follows: CT scans showed the presence and extent of polyps in the nasal cavity and sinuses in patients with chronic polypoid rhinosinusitis.

The endoscopic findings were as follows: Endoscopy provided direct visualization of nasal polyps, allowing assessment of their size, location, and extent. However, in five patients diagnosed with sinus polyps on CT scans, no polyps were identified on endoscopic examination.

- Ostiomeatal Complex Obstruction:

The CT findings were as follows: CT scans revealed ostiomeatal complex obstruction in 47 patients.

The endoscopic findings were as follows: endoscopy confirmed the presence of obstruction in the ostiomeatal complex, showing thick pus or polypoid tissue obstructing the drainage pathways.

2.3. Standardized Questionnaires

The Reflux Symptom Index (RSI), a nine-item self-administered questionnaire developed by Belafsky et al. (2002) [3], was used to document the presence and degree of symptoms of laryngopharyngeal reflux. The maximum score on the RSI is 45 [10].

The Reflux Symptom Score (RSS-12) 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 [11].

2.4. Endoscopic Assisment

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 [12,13], which graded 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

3.1. Demographics

Table 1 presents the descriptive statistics of the groups under consideration in terms of the sex of the subjects.

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

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.

Table 3 presents the results of comparing the means of age, RSS-12, and RSI between groups based on sex, race, and observation group. The *p*-value indicated whether the difference between the means was statistically significant. A *p*-value greater than 0.05 suggested that the means were 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] Kruskal–Wallis criterion for independent groups.

The Mann–Whitney U criterion for independent groups, noted as 1, was applied to determine significance. This non-parametric statistical criterion compared two independent samples on the level of a quantitatively measured characteristic. A smaller *p*-value suggested 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 was 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 was chosen due to the violation of the assumption of normality of

the data distribution in the groups. If the *p*-value was greater than 0.05, it indicated that there was no statistically significant difference between the medians.

3.2. Endoscopic Findings

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. 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 was 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%). This finding underscored the prevalence of nasal edema in our study population (see Figure 1A). However, discerning these findings as a specific characteristic of chronic rhinosinusitis associated with gastroesophageal disease in adults posed a challenge.

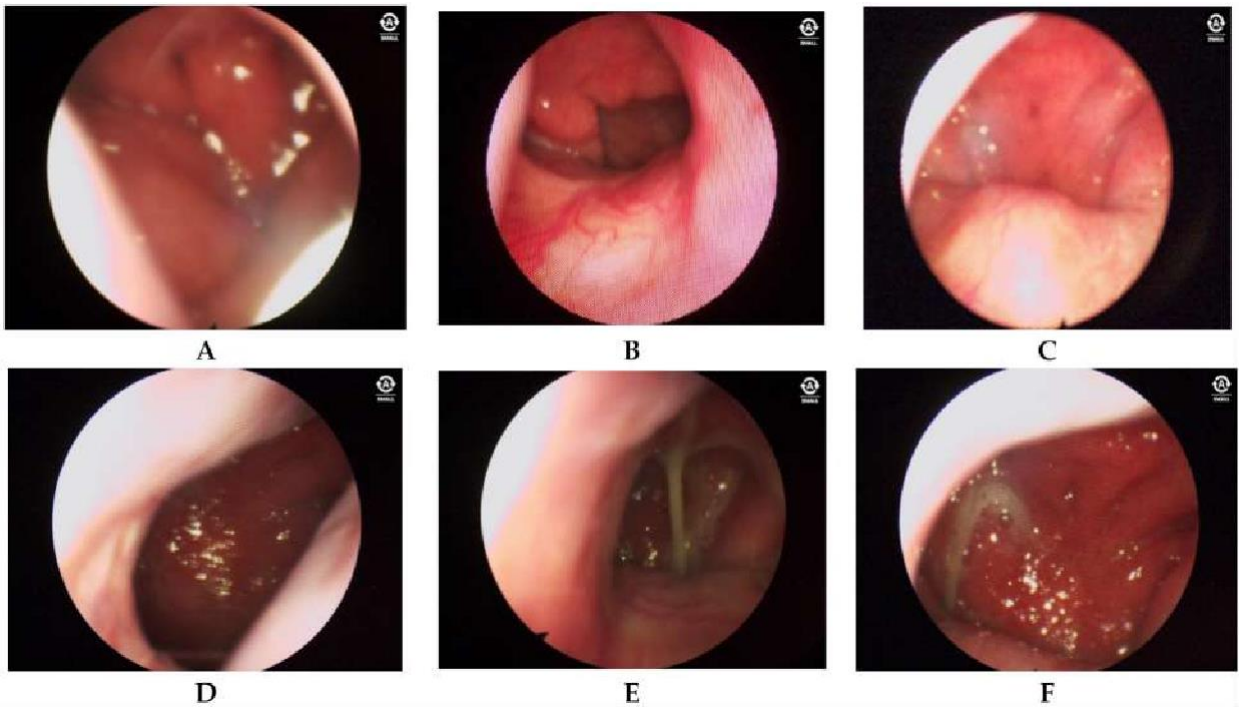

Figure 1. Endoscopic findings. A—Nasal edema. B,C—Increased vascularity. D—Hypertrophy of the nasopharyngeal mucosal layer. E—Mucus in the nasopharynx. F—Asymmetric hypertrophy of the mucosa of the oropharynx.

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 hypothesized 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 the left side. Therefore, we propose that these hypertrophic changes in the nose and nasopharynx may be induced by the effect of acidic reflux content.

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

Alterations in nasal cavity mucosa:

- Posterior nasal cavity: Distinct alterations in the mucosa are present, 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 are present.

Nasal edema:

- Nasal edema detected by two blinded raters is present in a significant percentage of patients (78.9%).

Nasopharyngeal mucosal alterations:

- Increased vascularity: This is noted in a majority of patients (95.7%), indicating possible inflammation or irritation.
- Hypertrophy: This is observed in a high percentage of patients (87.4%), suggesting chronic inflammation.
- Mucus production: This is 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 is 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 gastroesophageal reflux disease, contribute to the diagnosis of chronic rhinosinusitis associated with symptoms of gastroesophageal reflux disease in adults.

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

4. Discussion

Our study findings indicated that gastroesophageal reflux exerted 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 [14–17]. Analysis of the causal relationship between gastroesophageal reflux disease and chronic rhinosinusitis

at the genetic level has revealed that gastroesophageal reflux disease increases the risk of developing chronic rhinosinusitis by 36% [18].

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 [19], 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 [15]. 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 evi- denced 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 [20]. Another theory implicates Helicobacter pylori in the development of chronic rhinosinusitis, potentially leading to the formation of nasal polyps [21]. 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 [21].

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			

In addition to the above-mentioned results, we used the Camacho classification for the objective assessment of nasal cavity patency. In the second phase of our study, we plan to use the Lund–Kennedy endoscopic scoring system (LK) to objectively assess the severity of endoscopic manifestations in patients with chronic rhinosinusitis, both before treatment and after 8 weeks of therapy. The Lund–Kennedy scale rates polyps, discharge, edema, scarring, and crusting on a scale from 0 to 2 for each category, with higher scores indicating a more severe disease course. This scoring system is widely used in clinical practice and research to objectively assess the severity of chronic rhinosinusitis and track changes over time. It provides a standardized method to evaluate endoscopic findings,

facilitating comparison across studies and improving the accuracy of the diagnosis and treatment outcomes [22].

Several studies have investigated the relationship between chronic rhinosinusitis and gastroesophageal reflux disease using the Lund–Kennedy endoscopic scoring system. For example, a study in 2022 by Yeo et al. examined laryngopharyngeal reflux symptoms and signs in CRS patients, utilizing the Lund–Kennedy scale for endoscopic assessment. The study showed that subjective LPR symptoms were associated with subjective CRS symptoms. However, the researchers noted that Lund–Mackay scores did not significantly correlate with the preoperative Reflux Symptom Index and Reflux Finding Score [23]. Another study conducted by DelGaudio et al. (2005) established a significant association between extraesophageal reflux and increased endoscopic scores in CRS patients, suggesting that reflux might exacerbate nasal and sinus inflammation [24].

These findings align with previous research, which suggests that reflux, particularly extraesophageal reflux, contributes to the pathophysiology of chronic rhinosinusitis, potentially worsening the endoscopic appearance of the disease. This evidence underscores the importance of assessing and managing reflux symptoms in patients with chronic rhinosinusitis to potentially improve overall treatment outcomes.

5. Conclusions

Our comprehensive study, encompassing 95 patients with chronic rhinosinusitis accompanied by symptoms of gastroesophageal reflux disease along with two meticulously chosen control groups, illuminated profound alterations in the mucosal landscape of the posterior nasal and nasopharyngeal cavities. These discerning findings not only shed light on the intricate interplay between chronic rhinosinusitis and gastroesophageal reflux disease but 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 endeav- ors to deepen our understanding of this intricate relationship and optimize patient care strategies accordingly.

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The Diagnostic Accuracy of the Nasopharyngeal Reflux Endoscopic Score (NRES) for Identifying Laryngopharyngeal Reflux Disease in Chronic Rhinosinusitis

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Abstract: Background: Chronic rhinosinusitis with or without nasal polyps (CRSwNPs/CRSsNPs) is an inflammatory disease that is becoming increasingly associated with laryngopharyngeal reflux disease (LPRD). Although symptom-based questionnaires, such as the Reflux Symptom Index (RSI) and Reflux Symptom Score (RSS), are widely used, there is a lack of objective endoscopic tools for assessing the nasopharyngeal and nasal manifestations of reflux. The Nasopharyngeal Reflux Endoscopic Score (NRES) is a novel endoscopic scoring system that was developed to address this issue. Objective: The objective of this study was to evaluate the diagnostic accuracy of the NRES in identifying LPRD in patients with CRS, compared with a clinical reference standard. **Methods**: A prospective diagnostic accuracy cohort study was conducted at two tertiary care centers in Astana, Kazakhstan, from September 2023 to February 2025. A total of 216 adults were enrolled and divided into three groups: CRS with suspected LPRD (n = 116), CRS without LPRD (n = 69), and healthy controls (n = 31). CRS was diagnosed according to the EPOS 2020 criteria. LPRD was defined using a composite reference standard comprising clinical assessment, RSS > 13, RSI, and selective 24 h pH monitoring and gastrointestinal endoscopy. All participants underwent nasopharyngeal and laryngeal endoscopy, with NRES, L-K, RFS, RSI, and RSS assessments at baseline and at 6 and 12 months. Receiver operating characteristic (ROC) analysis was used to evaluate the diagnostic performance, and Wilcoxon tests were used to analyze the changes in scores. Correlation and regression analyses were used to explore associations between scales and predictive factors. **Results**: At baseline, NRES scores were significantly higher in the CRS with LPRD group (mean: 11.59) than in the CRS without LPRD group (mean: 3.10) and the healthy control group (mean: 2.16) ($p < 0.001$). ROC analysis demonstrated excellent diagnostic accuracy, with an area under the curve (AUC) of 0.998 (95% confidence interval (CI): 0.994–1.000), a sensitivity of 98% (95% CI: 94–100%) and a specificity of 96% (95% CI: 91–99%) at an optimal cut-off point of 8.5. NRES scores showed strong correlations with RSI, RSS, and RFS scores ($r > 0.76$, $p < 0.001$). A longitudinal assessment revealed significant reductions in all scores after treatment with proton pump inhibitors and lifestyle modifications, with sustained improvement at 12 months. Regression analysis found no significant effect of age, gender, or GERD severity (LA classification) on NRES scores. **Conclusions**: The NRES is a highly sensitive and specific endoscopic tool for identifying nasopharyngeal changes

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associated with LPRD in CRS patients. It demonstrates strong correlations with established symptom-based and laryngoscopic reflux assessments and responds to anti-reflux therapy over time. The NRES may, therefore, be a valuable objective adjunct in the comprehensive evaluation and longitudinal monitoring of LPRD-associated CRS.

Keywords: chronic rhinosinusitis with or without nasal polyps (CRSwNPs/CRSsNPs); laryngopharyngeal reflux disease; the Nasopharyngeal Reflux Endoscopic Score (NRES); the Reflux Symptom Index (RSI); the Reflux Symptom Score (RSS)

1. Introduction

Chronic rhinosinusitis (CRS), with or without nasal polyps (CRSwNPs/CRSsNPs), is a multifactorial inflammatory condition affecting the nasal and paranasal sinuses. It is often resistant to conventional medical and surgical treatments [1–3]. There is an increasing body of evidence linking CRS with laryngopharyngeal reflux disease (LPRD), which is distinct from gastroesophageal reflux disease (GERD) because of its primary impact on the upper aerodigestive tract [3,4]. GERD has been linked to various extraesophageal manifestations, including laryngitis, chronic cough, asthma, otitis media with effusion, and, more recently, CRS. Studies estimate that up to 60% of CRS patients exhibit LPRD features, suggesting significant overlap [5–7].

The proposed mechanism by which LPRD contributes to CRS involves the direct exposure of the nasopharyngeal and sinus mucosa to refluxed gastric contents, including acid and pepsin. This exposure disrupts epithelial integrity, impairs mucociliary clearance, and sustains chronic inflammation [8,9]. Histopathological findings, including epithelial hyperplasia, goblet cell metaplasia, and inflammatory infiltration, further support reflux as a contributor to remodeling and dysfunction of the sinuses [9,10].

However, diagnosing LPRD-associated CRS remains clinically challenging because of the overlap of symptoms with those of allergic or infectious rhinitis and the limitations of current diagnostic tools. Objective methods, such as 24 h multichannel intraluminal impedance-pH (MII-pH) monitoring, assess esophageal reflux but provide limited insight into nasopharyngeal or sinus exposure [11,12]. Symptom-based tools, such as the Reflux Symptom Index (RSI) and Reflux Symptom Score (RSS), rely on subjective reporting and fail to capture observable mucosal pathology. Similarly, the Reflux Finding Score (RFS), a validated endoscopic tool for laryngeal signs of reflux, lacks specificity for nasopharyngeal and sinus involvement [13].

In order to address these diagnostic limitations, we developed the Nasopharyngeal Reflux Endoscopic Score (NRES), a standardized endoscopic tool designed to objectively evaluate changes to the nasopharyngeal mucosa associated with LPRD. The NRES evaluates parameters such as erythema, edema, mucus congestion, and mucosal granularity, which reflect reflux-induced inflammation that is often overlooked by esophageal-focused diagnostics. As an addition to the existing symptom-based and laryngeal assessment tools, the NRES aims to improve diagnostic accuracy, enable the early detection of reflux-related sinus and nasal disease, and inform personalized treatment strategies for CRS patients with suspected LPRD.

This study aims to evaluate the diagnostic accuracy of the NRES in identifying LPRD in patients with CRS using a composite clinical reference standard based on RSI, RSS, clinical assessment, and selective pH monitoring or endoscopy. We hypothesize that the NRES will demonstrate high sensitivity and specificity in distinguishing CRS associated

with LPRD from CRS without LPRD and from healthy controls, thereby offering clinicians a reliable, objective tool.

2. Materials and Methods

The study protocol was approved by the Local Ethics Committee of Astana Medical University, Astana, Kazakhstan (Approval Number: LCB AMU #13). Written informed consent was obtained from all participants. The anonymized study dataset is publicly available at https://doi.org/10.6084/m9.figshare.28861565, accessed on 25 April 2025.

2.1. Study Design

This was a prospective, observational, comparative cohort study with longitudinal follow-up. It was conducted from September 2023 to February 2025 at two tertiary care centers in Astana, Kazakhstan: the University Medical Centre Corporate Fund (UMC CF) and Multidisciplinary Hospital No. 1.

2.2. Participants

Consecutive adults aged ≥18 years presenting with chronic nasal symptoms persisting for at least 12 months were screened for eligibility. The inclusion criteria included a diagnosis of chronic rhinosinusitis (CRS), with or without nasal polyps (CRSwNPs or CRSsNPs), based on the 2020 European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2020) criteria [14]. This encompasses clinical symptoms, nasal endoscopy using the Lund–Kennedy (L-K) score, and computed tomography (CT) imaging findings. The exclusion criteria included recent nasal surgery (within six months), other diseases affecting the sinuses (e.g., tumors or granulomatous diseases), or an inability to provide informed consent. Healthy controls were age- and sex-matched volunteers without any symptoms of sinus disease or known reflux disease. The participants were stratified into three groups based on the reference standard for laryngopharyngeal reflux disease (LPRD):

CRS with LPRD (n = 116);
CRS without LPRD (n = 69);
Healthy controls (n = 31).
Reference standard for LPRD.

The reference standard for diagnosing LPRD was a composite assessment by an otolaryngologist and a gastroenterologist. This was based on a clinical evaluation and the following:

- The Reflux Symptom Score (RSS) with a cut-off of >13 [15].
- The Reflux Symptom Index (RSI) [16].
- Physician judgment incorporating symptom patterns and response to proton pump inhibitor (PPI) therapy. In cases where diagnosis was uncertain, 24 h dual-probe pH monitoring and gastrointestinal endoscopy were performed to confirm gastroesophageal reflux disease (GERD) and characterize the reflux phenotype. The assessors were blinded to the Nasopharyngeal Reflux Endoscopic Score (NRES) results.

Index test: Nasopharyngeal Reflux Endoscopic Score (NRES).

The NRES is a novel endoscopic scoring system designed to detect nasopharyngeal mucosal changes suggestive of extraesophageal reflux (see Table 1). It assesses the follow- ing signs: asymmetry in the nasal cavity; hypertrophy of the inferior turbinate; absence of mucus; hypertrophy of the nasopharyngeal wall and Eustachian tube opening; increased vascular pattern; presence of mucus; erythema; atrophic changes; and granulations or fibrotic changes. Each sign is scored as 0 (absent), 1 (moderately expressed), or 2 (severely expressed), and the total score is then summed. Standardized fiberoptic nasopharyn- goscopy with digital photo documentation was performed at each visit. Two independent

otolaryngologists, blinded to the patients' symptom scores and clinical group, evaluated the images and resolved any discrepancies by consensus.

Table 1. Nasopharyngeal Reflux Endoscopic Score (NRES).

Signs of Nasopharyngeal Reflux Exposure	0 (Absent)	1 (Moderately Expressed)	2 (Severely Expressed)
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 tube opening	□	□	□
Increased vascular pattern	□	□	□
Presence of mucus	□	□	□
Erythema or inflammation of the nasopharyngeal mucosa	□	□	□
Atrophic changes in the mucosa	□	□	□
Presence of granulations or fibrotic changes	□	□	□

Table 1 shows the Nasopharyngeal Reflux Endoscopic Score (NRES), which is a standardized system for evaluating signs of nasopharyngeal reflux detected during an endoscopic examination. These signs are categorized by anatomical location as either 'nose' or 'nasopharynx'. Each sign is graded according to its severity and given a score from 0 to 2, where 0 (absent) indicates that the sign is not observed; 1 (moderately pronounced) indicates that the trait is present but not pronounced; and 2 (strongly pronounced) indicates that the trait is clearly or significantly pronounced. The checkmarks (□) under each score (0, 1, or 2) show the possible scores for each feature. The appropriate score is selected based on endoscopy data. The total NRES score is calculated by adding together the scores for all the individual features in order to determine the overall severity of nasopharyngeal reflux.

2.3. Data Collection

At baseline, all the participants underwent a comprehensive examination, including fiberoptic rhinoscopy with photo documentation, transnasal fiberoptic laryngoscopy, and assessments using the NRES, L-K score, and Reflux Finding Score (RFS). Symptom scores (RSS and RSI) were collected. Patients diagnosed with LPRD received 20 mg of omeprazole twice daily for one to two months after the visit, alongside lifestyle modifications to mitigate GERD symptoms. Follow-up assessments at six and twelve months involved repeating the baseline examinations. A second clinic visit within one week of each assessment ensured consistency.

2.4. Blinding

The assessors who determined the LPRD reference standard were blinded to the NRES results, and the otolaryngologists who scored the NRES were blinded to the clinical data and reference standard outcomes.

2.5. Statistical Methods

The diagnostic accuracy of the NRES was evaluated using a receiver operating characteristic (ROC) analysis of the baseline data. The area under the curve (AUC), as well as the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), were calculated at an optimal cut-off point, which was determined using the Youden index. Between-group differences at baseline were assessed using the Kruskal–Wallis test, followed by Dunn's test with Bonferroni adjustment for pairwise comparisons. Longitudinal changes in the LPRD group were analyzed using paired Wilcoxon tests with Holm's correction at baseline and at the 6- and 12-month time points. Spearman's rank correlation was used to assess the associations between the NRES, RSS, RSI, RFS, and L-K scores. Multiple linear regression evaluated the dependence of the NRES on age, gender, and GERD severity (Los Angeles classification). Participants with missing baseline data for the NRES or the reference standard were excluded from the analysis of diagnostic accuracy; the longitudinal analysis included only those with complete follow-up data. Analyses were performed using IBM SPSS Statistics 25, with $p < 0.05$ being considered significant.

3. Results

3.1. Participant Flow and Baseline Characteristics

Between September 2023 and February 2025, a total of 250 participants were screened for eligibility. Of these, 216 met the inclusion criteria and were enrolled: 116 had chronic rhinosinusitis (CRS) and laryngopharyngeal reflux disease (LPRD) (Group 1); 69 had CRS but not LPRD (Group 2); and 31 were healthy controls (Group 3). All the participants completed the baseline assessment, with no indeterminate results or loss to follow-up reported for the index test (Nasopharyngeal Reflux Endoscopic Score, NRES) or reference standard. Baseline demographic and clinical characteristics are summarized in Table 2.

Table 2. Baseline characteristics of the study participants.

Characteristic	Group 1: CRS with LPRD (n = 116)	Group 2: CRS Without LPRD (n = 69)	Group 3: Healthy Controls (n = 31)
Age, mean (SD), years	45.2 (12.3)	44.8 (11.9)	43.5 (10.7)
Female, n (%)	68 (58.6%)	39 (56.5%)	18 (58.1%)
CRS with nasal polyps, n (%)	52 (44.8%)	30 (43.5%)	N/A

Table 2 shows the baseline demographic and clinical characteristics of the study participants, divided into three groups. Group 1: CRS with LFRH (n = 116), including the participants diagnosed with both chronic rhinosinusitis (CRS) and laryngopharyngeal reflux disease (LPRD). Group 2: CRS without LFRZ (n = 69), including the participants diagnosed with CRS but not LPRD. Group 3: Healthy control participants (n = 31), including healthy individuals who did not have a diagnosis of CRS or LFRZ and who served as the control group. The table below shows the characteristics of each group. Age (mean (SD)) in years: The mean age of the participants in each group, where the standard deviation (SD) shows the variation in ages within the group. Women, n (%): The number and percentage of women in each group.

CRS with nasal polyps: The number and percentage of participants with CRS and nasal polyps. For group 3 (healthy control participants), this indicator is not applicable (N/A), as they do not have CRS.

The Kruskal–Wallis H test was used to evaluate differences in reflux- and sinus-related indicators across the three groups, as this is a non-parametric method suitable for non-normally distributed data. Statistically significant differences were observed for the Reflux Symptom Score (RSS), Reflux Symptom Index (RSI), Reflux Finding Score (RFS), Nasopharyngeal Reflux Endoscopic Score (NRES), and Lund–Kennedy (L-K) score (all $p < 0.0001$).

Post hoc pairwise comparisons using Dunn's test with Bonferroni adjustment revealed that Group 1 (CRS with LPRD) had significantly higher RSS, RSI, RFS, and NRES scores than Groups 2 (CRS without LPRD) and 3 (healthy controls) (all $p < 0.0001$). No significant differences were found between Groups 2 and 3 for these parameters ($p > 0.05$), suggesting that elevated reflux-related and nasopharyngeal findings were specific to the patients with CRS and LPRD. For the L-K score, no significant difference was observed between Groups 1 and 2 ($p = 0.888$), indicating comparable sinus inflammation in the CRS patients regardless of LPRD status. However, Groups 1 and 2 both had significantly higher L-K scores than Group 3 ($p < 0.0001$). Detailed distributions are shown in Figure 1.

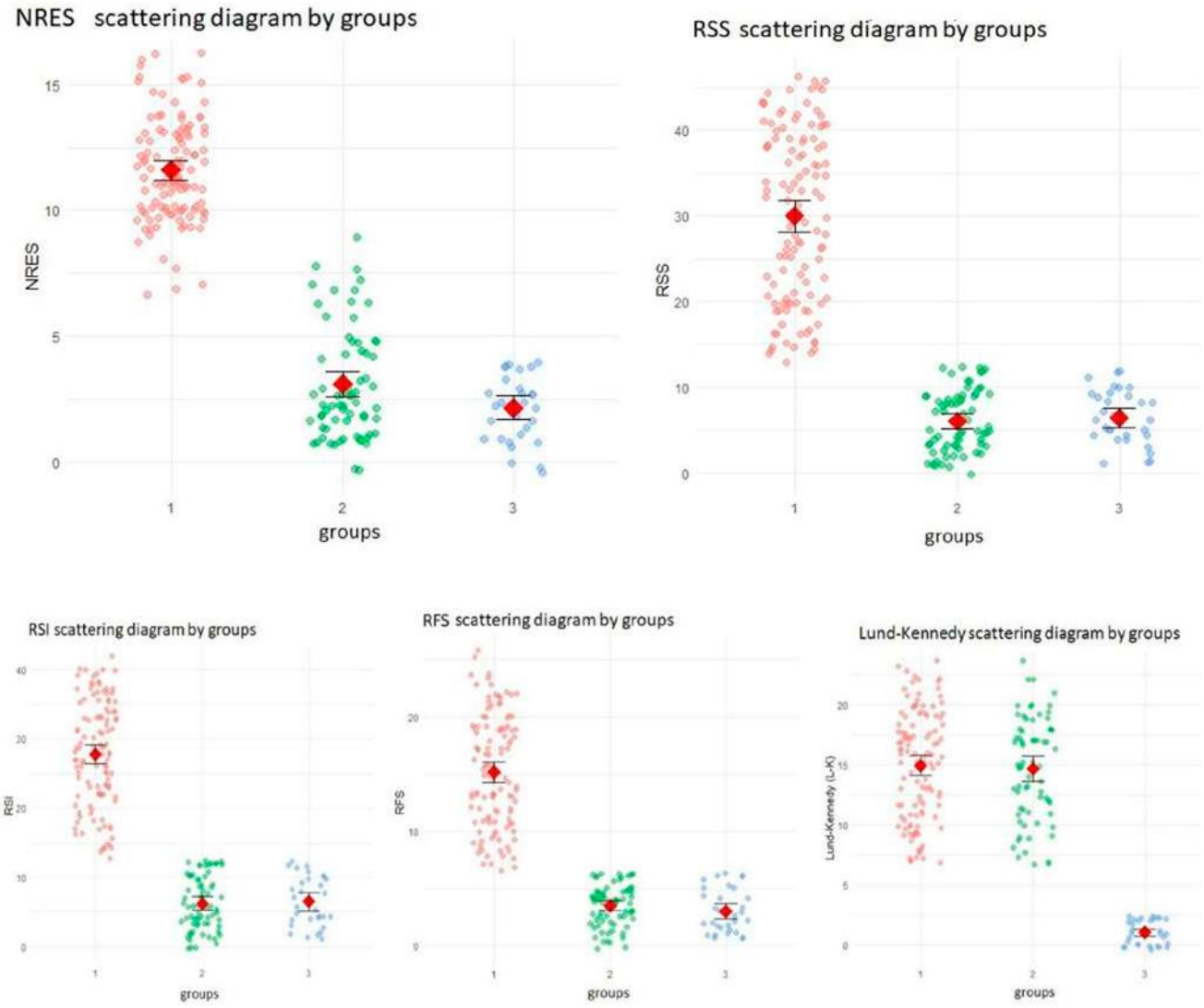

Figure 1. Boxplots of baseline scores across the study groups. NRES Scattering Diagram by groups. Figure 1 uses a scatter diagram to illustrate the distribution of baseline Nasopharyngeal Reflux Endoscopic Score (NRES) values across the three distinct study groups. The groups are defined as follows: Group 1: patients with chronic rhinosinusitis (CRS) and laryngopharyngeal reflux disease (LPRD); Group 2: patients with CRS without LPRD; and Group 3: healthy controls. This figure visually compares NRES scores to assess the diagnostic accuracy of the NRES in identifying LPRD among CRS patients. Each data point represents an individual NRES score, and summary statistics are highlighted for each group. Axes: The X-axis is labeled 'groups', with categories 1, 2, and 3 corresponding to the study groups described above. The Y-axis is labeled 'NRES', with a range from 0 to 15 representing the NRES score values. Visual elements: Colored dots: Individual NRES scores are plotted as colored dots. Pink dots represent scores for Group 1 (CRS with LPRD) and show a

dense cluster ranging from approximately 5 to 15. Green dots represent scores for Group 2 (CRS without LPRD) and are distributed between 0 and 10. Blue dots represent scores for Group 3 (healthy controls), concentrated near 0 with values typically between 0 and 3. The distinct colors differentiate the groups, highlighting variations in NRES scores across the populations. Red diamonds indicate the mean NRES score for each group: Group 1 is positioned around 10–12, reflecting a higher average NRES score; Group 2 is positioned around 5–7, indicating a moderate average score; and Group 3 is positioned around 2–3, showing the lowest average score. Group-specific observations: Group 1 (CRS with LPRD) displays a broad range of NRES scores (5–15) and a higher mean (red diamond at 10–12), suggesting signs of elevated nasopharyngeal reflux consistent with LPRD. Group 2 (CRS without LPRD) shows a more moderate range (0–10), with an average score of around 5–7. This indicates that the NRES scores are lower than in Group 1. Group 3 (healthy controls) exhibits minimal NRES scores (0–3) with an average of around 2–3, reflecting an absence of significant reflux symptoms in healthy individuals.

The diagnostic accuracy of the NRES in identifying LPRD-associated CRS was assessed using a receiver operating characteristic (ROC) curve. This analysis included all 216 participants. Group 1 (CRS with LPRD, n = 116) was classified as 'disease present' (coded as 1), while Groups 2 (CRS without LPRD, n = 69) and 3 (healthy controls, n = 31) were classified as 'disease absent' (coded as 0). The area under the curve (AUC) was 0.998 (95% CI: 0.994–1.000), indicating exceptional discriminatory ability. At the optimal cut-off point of NRES ≥8.5 (as determined by the Youden index), the sensitivity was 98% (95% CI: 94–100%) and the specificity was 96% (95% CI: 91–99%). The positive predictive value (PPV) was 97% (95% CI: 93–99%), and the negative predictive value (NPV) was 97% (95% CI: 92–99%). These results suggest that the NRES is a reliable tool for identifying LPRD-associated CRS. The results are summarized in Table 3.

Table 3. Diagnostic accuracy of the NRES at the optimal cut-off (NRES ≥ 8.5).

Metric	Estimate (95% CI)
AUC	0.998 (0.994–1.000)
Sensitivity	98% (94–100%)
Specificity, True Negative Rate, TNR	96% (91–99%)
Positive Predictive Value	97% (93–99%)
Negative Predictive Value	97% (92–99%)

Table 3 contains the key metrics for the diagnostic accuracy of the Nasopharyngeal Reflux Endoscopic Score (NRES), with an optimal threshold value of 8.5 or above. These metrics evaluate the NRES's ability to detect laryngopharyngeal reflux (LPRD) in patients with chronic rhinosinusitis (CRS).

3.2. Longitudinal Changes in Scores

Changes in the NRES, RSS, RSI, RFS, and L-K scores were assessed in Group 1 (n = 116) at six and twelve months following treatment. Paired Wilcoxon tests with Holm's correction revealed significant reductions in all scores from baseline to six months and from baseline to 12 months (all $p < 0.001$). Further improvements between six and twelve months were significant for the NRES ($p = 0.017$), RSS ($p < 0.001$), and L-K ($p < 0.001$), indicating sustained treatment effects. Figure 2 illustrates the dynamics.

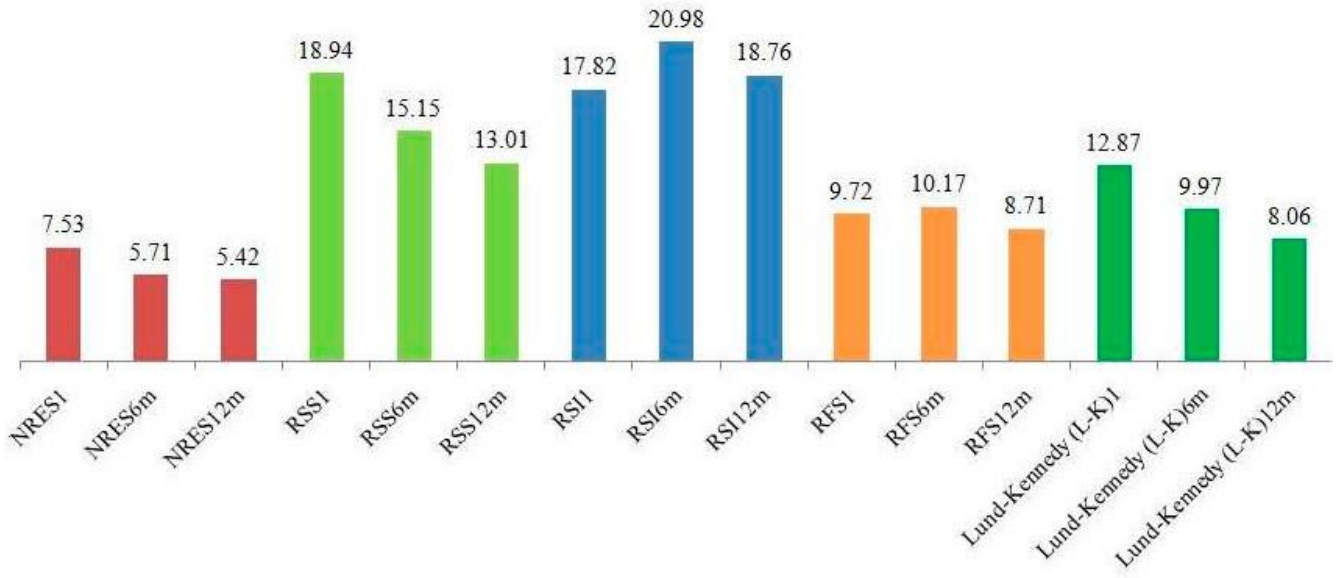

Figure 2. Longitudinal changes in scores at baseline, 6 months, and 12 months for the study groups. This figure presents a bar chart showing the mean values of various indicators for the three study groups at different time points after treatment application: baseline, six months, and 12 months. The indicators include the Nasopharyngeal Reflux Endoscopic Scale (NRES), the Reflux Symptom Index (RSI), the Reflux Symptom Score (RSS), the Reflux Findings Score (RFS), the Lund–Kennedy Scale (LKS), and the Los Angeles (LA) Classification for gastroesophageal reflux disease (GERD) severity. The groups are distinguished by column color, and the heights of the columns reflect the mean values. Axes: The X-axis shows the indicator categories and time points, including NRES1, NRES6m, and NRES12m, representing the NRES at baseline and at 6 and 12 months; RSS1, RSS6m, and RSS12m, representing the RSS at baseline and after 6 and 12 months; RSI1, RSI6m, and RSI12m, representing the RSI at baseline, after 6 months, and after 12 months; and LA1, LA6m, and LA12m, representing the LA classification at baseline and at 6 and 12 months. The Y-axis shows the mean values of the indicators, scaled from 0 to 25, with each value reflecting the mean group score. Color coding: Red: Group 1 (CRS and LFRH patients) at baseline (e.g., NRES1 = 7.5, RSS1 = 5.7). Green: Group 1 (CRS and LFRZ patients) at 6 and 12 months (e.g., NRES6m = 18.9, RSS6m = 21.0; NRES12m = 15.2, RSS12m = 17.8). Blue: Group 2 (CRS patients without LFRH) after 6 months (e.g., RSI6m = 18.8) and after 12 months (e.g., RSI12m = 13.0). Orange: Group 3 (healthy control subjects) after 6 months (e.g., RFS6m = 9.7) and after 12 months (e.g., RFS12m = 10.2). Green (additional shading): Group 3 after 12 months for certain indicators (e.g., L-K12m = 12.9 and LA12m = 10.0).

3.3. Correlation Across Scales

Spearman's correlation analysis was conducted to explore the relationships between the NRES, RSS, RSI, RFS, and L-K scores at baseline. Strong positive correlations were observed between the NRES and RSS ($r = 0.768$, $p < 0.001$), RSI ($r = 0.766$, $p < 0.001$), and RFS ($r = 0.769$, $p < 0.001$), which supports the convergent validity of the NRES. A weaker correlation was found with L-K ($r = 0.221$, $p < 0.01$), indicating that the NRES captures changes specific to reflux rather than general sinus inflammation. The results are presented in Table 4.

Table 4. Spearman correlation matrix.

	NRES	RSS	RSI	RFS	Lund–Kennedy (L-K)
NRES	1.000	0.768 *	0.766 *	0.769 *	0.221 *
RSS	0.768 *	1.000	0.787 *	0.729 *	0.242 *
RSI	0.766 *	0.787 *	1.000	0.758 *	0.278 *
RFS	0.769 *	0.729 *	0.758 *	1.000	0.284 *
Lund–Kennedy (L-K)	0.221 *	0.242 *	0.278 *	0.284 *	1.000

* Correlation is significant at the 0.01 level. Table 4 presents the Spearman correlation matrix demonstrating the relationships between the various indices measured at the start of this study. These include the Nasopharyngeal Reflux Endoscopic Scale (NRES), the Reflux Symptom Score (RSS), the Reflux Symptom Index (RSI), and the Reflux Findings Score (RFS), as well as the Lund–Kennedy (L-K) scale. The matrix shows the strength and direction of the associations between these scales, which is important for understanding their interrelationships and the diagnostic value of the NRES.

3.4. Regression Analysis

Multiple linear regression was performed to examine the relationship between the baseline NRES scores and clinical variables (age, race, Los Angeles (LA) classification of GERD severity) in Group 1 (n = 116). The model yielded an R^2 of 0.061 (adjusted R^2 = 0.018), indicating low explanatory power, and was not statistically significant (F = 1.419, p = 0.223). No predictors—age (p = 0.156), race (p = 0.272), or LA classification (p > 0.05)—were significantly associated with the NRES scores, though a trend toward lower scores in LA category C (p = 0.060) was noted. The results are detailed in Table 5.

Table 5. Regression results.

Term	Estimate	Std. Error	Statistic	*p* Value
(Intercept)	12.94621936	0.766071047	16.89950222	0.000
age	−0.02046886	0.014314153	−1.429973523	0.156
race	−0.452673187	0.40994756	−1.104222178	0.272
LA Classification B	−0.153630492	0.432067518	−0.355570567	0.723
LA Classification C	−1.023346692	0.537950794	−1.902305385	0.060
LA Classification D	−0.860190641	1.46213281	−0.588312248	0.558

Table 5 shows the results of a multiple linear regression analysis that was carried out to evaluate the correlation between the initial scores on the Nasopharyngeal Reflux Endoscopic Scale (NRES) and various clinical factors in Group 1 (patients with chronic rhinosinusitis and laryngopharyngeal reflux, n = 116). The model included the following predictors: age, race, and the Los Angeles Classification (LA Classification) for the severity of gastroesophageal reflux disease (GERD). The model's overall R^2 was 0.061 (adjusted R^2 = 0.018), indicating low explanatory power. The model, as a whole, was not statistically significant (F = 1.419, p = 0.223).

4. Discussion

Chronic rhinosinusitis with or without nasal polyps and laryngopharyngeal reflux disease (LPRD) are interrelated conditions that may reinforce each other via shared pathological mechanisms. CRS is characterized by long-term inflammation of the nasal and paranasal mucosa, while LPRD occurs when gastric contents enter the upper respira- tory tract and cause irritation and inflammation. Understanding these mechanisms is crucial for developing effective diagnostic and therapeutic strategies, such as using the Nasopharyngeal Reflux Endoscopic Score (NRES) [14]. Its pathophysiology is multifactorial, encompassing infectious, allergic, environmental, and, increasingly, reflux-related mechanisms [17]. Over the past two decades, extraesophageal reflux (EER)—the retrograde flow of gastric contents beyond the esophagus into the larynx, pharynx, nasopharynx,

and, potentially, the sinus cavities—has gained attention as a contributor to upper airway disease, including CRS [18–23]. Unlike classical gastroesophageal reflux disease (GERD), EER can involve acidic or non-acidic refluxate, which can promote pathology by causing direct epithelial injury, mucociliary dysfunction, disruption to the epithelial barrier, and sustained mucosal inflammation [24–29].

CRS and LPRD reinforce each other through the following pathogenetic mechanisms:

Increased inflammation by reflux: Research suggests that when stomach acid and pepsin enter the nasopharynx following reflux, they activate inflammatory pathways. This increases the production of cytokines, such as IL-6 and TNF-α, which attract immune cells and exacerbate CRS, particularly in refractory cases [1,30,31]. Studies such as that by Liu et al. (2021) demonstrate how LPR can lead to inflammatory responses in the upper aerodigestive tract, including the sinuses, thus supporting this mechanism [30]. Lechien et al. (2023) further confirm that reflux contributes to inflammation in CRS, especially in recalcitrant cases [1].

The vicious circle of mucociliary dysfunction: It is thought that mucus stagnation in the sinuses of people with CRS can promote reflux, creating a cycle. In turn, reflux damages the ciliated epithelium, impairing the body's ability to clear mucus and maintaining chronic inflammation and symptoms in both conditions. Prithviraj et al. (2024) discuss how LPR contributes to CRS through such mechanisms, emphasizing the cycle's impact [32].

Epithelial vulnerability: There is evidence that reflux damages the epithelium, reducing its barrier properties and making the mucosa more susceptible to infections and allergens, thus exacerbating CRS [1,30]. Liu et al. (2021) directly address how LPR leads to mucosal barrier dysfunction, thereby increasing vulnerability to infections and allergens [30]. This aligns with the aforementioned mechanism. This damage creates a feedback loop that worsens CRS symptoms and inflammation.

Immune modulation: Studies indicate that reflux can enhance Th2-mediated inflammation, which is characteristic of CRSwNPs (CRS with nasal polyps), and this could contribute to polyp formation and chronicity. Zhang et al. (2019) [33] discuss the role of Th2 cytokines in chronic rhinosinusitis with nasal polyps (CRSwNPs), suggesting that reflux could influence this immune response; however, more research is needed to confirm any direct links. Reflux can modulate immune responses, particularly by enhancing Th2-mediated inflammation, which is characteristic of CRSwNPs, as noted by Zhang et al. (2019) [33]. This can contribute to polyp formation and the chronic nature of the disease.

Aldajani et al. (2024) provide evidence of an association between reflux diseases and CRS, supporting the potential for immune modulation [2]. However, direct links require further research.

The literature provides strong evidence of the pathogenetic mechanisms linking chronic rhinosinusitis (CRS) and laryngopharyngeal reflux disease (LPRD), including increased inflammation, mucociliary dysfunction, epithelial vulnerability, and immune modulation. These mechanisms create a reinforcing cycle that exacerbates both conditions, emphasizing the importance of tools such as NRES for diagnosis and management, as it detects the specific changes to the nasopharyngeal mucosa associated with reflux. NRES allows clinicians to objectively assess inflammation caused by LPRD and differentiate it from other causes of CRS. This information can inform treatment decisions, including the use of anti-reflux therapies, such as proton pump inhibitors, as well as lifestyle modifications, both of which could potentially improve patient outcomes.

However, diagnosing CRS associated with laryngopharyngeal reflux disease (LPRD) remains challenging because of symptom overlap with allergic rhinitis, non-allergic rhinitis, and primary CRS, which often leads to misdiagnosis or underdiagnosis [22,30]. Although symptom-based tools, such as the Reflux Symptom Index (RSI) and Reflux Symptom

Score (RSS), are validated for quantifying reflux-related symptoms, their subjective nature limits their ability to assess mucosal changes directly [15,16]. Objective methods, such as 24 h esophageal pH monitoring and multichannel intraluminal impedance–pH (MII- pH) testing, are the gold standard for esophageal reflux [18,27], but they do not evaluate nasopharyngeal or sinus exposure. Similarly, the Reflux Finding Score (RFS), an endoscopic tool for laryngeal signs of reflux, lacks specificity for nasopharyngeal pathology [16].

In order to address this diagnostic gap, we developed the Nasopharyngeal Reflux Endoscopic Score (NRES), a standardized endoscopic tool for assessing nasopharyngeal mucosal changes linked to reflux. The NRES evaluates parameters such as erythema, edema, mucus congestion, and granularity, which are markers of chronic irritation and the epithelial response to reflux exposure. The primary aim of this study was to evaluate the diagnostic accuracy and clinical utility of the NRES in identifying laryngopharyngeal reflux disease (LPRD)-associated chronic rhinosinusitis (CRS). We hypothesized that the NRES would demonstrate high sensitivity and specificity in distinguishing CRS cases with nasopharyngeal reflux from other phenotypes. Our findings confirmed this, showing that the NRES is a reliable and reproducible tool for detecting LPRD-related nasopharyn- geal changes.

4.1. Clinical Applicability of the NRES

The NRES is intended to complement existing diagnostic tools for CRS patients with suspected LPRD. Its ability to objectively assess nasopharyngeal inflammation enhances diagnostic precision, particularly in cases where symptoms are non-specific or do not respond to standard CRS treatments. In clinical practice, the NRES can be incorporated into the diagnostic process for patients presenting with symptoms such as persistent nasal obstruction, postnasal drip, or throat discomfort that suggest LPRD. By providing a standardized scoring system, the NRES enables consistent documentation of endoscopic findings and supports targeted therapeutic strategies, such as anti-reflux therapy. This could improve patient outcomes by identifying those who are likely to benefit from reflux management and reducing the need for prolonged empirical treatments.

Implementing the NRES requires fiber-optic nasopharyngoscopy and otolaryngologists who are trained in the scoring criteria. While this may present challenges in settings with limited resources, the potential for improved diagnostic accuracy and personalized treatment justifies efforts to increase its use. As this study was conducted in Kazakhstan, it remains to be confirmed whether the NRES can be generalized to other populations and healthcare systems. Validation in diverse demographic and clinical contexts would strengthen its applicability.

4.2. Limitations and Future Directions

A significant limitation of this study is the absence of hypopharyngeal–esophageal MII-pH monitoring, which is the gold standard for confirming LPRD. While MII-pH is effective at detecting esophageal reflux, it does not assess nasopharyngeal exposure. This highlights the need for complementary tools like the NRES. Future research should incorporate MII- pH to validate the NRES against this standard and explore correlations between esophageal and nasopharyngeal reflux events. Furthermore, larger multicenter studies are required to evaluate the performance of the NRES across different populations and refine its scoring parameters to achieve optimal sensitivity and specificity. Although research supports the association between CRS and LPRD, the exact mechanisms of their interaction remain poorly understood. For instance, the impact of non-acid reflux on the nasopharyngeal microbiome requires further investigation. Furthermore, studies are needed to determine

whether early detection of reflux using tools such as the NRES can prevent the progression of CRS or reduce the need for surgical intervention.

5. Conclusions

The NRES is a significant advance in the diagnosis of LPRD-associated CRS, providing an objective and reproducible method that fills the gap left by existing tools. Its clinical applicability lies in enhancing diagnostic accuracy, guiding treatment decisions, and improving outcomes for patients with reflux-related upper airway disease. As further validation refines its utility, the NRES has the potential to become a cornerstone in the management of this challenging condition.

Author Contributions: Conceptualization, K.S. and N.P.; methodology, K.S.; software, K.S.; validation, G.M. and T.A.; formal analysis, K.S.; investigation, K.S., N.P., G.M. and T.A.; resources, K.S.; data curation, K.S. and N.P.; writing—original draft preparation, K.S.; writing—review and editing, J.R.L.; visualization, K.S.; supervision, N.P.; project administration, K.S.; funding acquisition, K.S. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. The study protocol was reviewed and approved by the Local Ethics Committee of Astana Medical University (Ethical Approval Number: LCB AMU #13, 29 November 2023).

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

Data Availability Statement: The data presented in this study are openly available in https://doi.org/10.6084/m9.figshare.28861565 (accessed on 25 April 2025).

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

Abbreviations

The following abbreviations are used in this manuscript:

CRSwNP/CRSsNP	chronic rhinosinusitis with or without nasal polyps
LPRD	laryngopharyngeal reflux disease
RSI	Reflux Symptom Index
RSS	Reflux Symptom Score
NRES	Nasopharyngeal Reflux Endoscopic Score
L-K	Lund–Kennedy
EPOS	European Position Paper on Rhinosinusitis and Nasal Polyps 2020
RFS	Reflux Finding Score
ROC	receiver operating characteristic
PPIs	proton pump inhibitors
GERD	gastroesophageal reflux disease
MII-pH	multichannel intraluminal impedance–pH
EER	extraesophageal reflux

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ПРИЛОЖЕНИЕ А

Акт внедрения

АКТ

Внедрения результатов научно - исследовательской работы
ГКП на ПХВ «Городская поликлиника №11» акимата г. Астана

Наименование предложения: Алгоритм диагностики и лечения пациентов с рефлюкс-ассоциированным хроническим риносинуситом.

Работа включена: из плана внедрений научно-исследовательских работ НАО «Медицинский Университет Астана», алгоритм разработан докторантом.

Форма внедрения: Новый алгоритм ведения пациентов с рефлюкс-ассоциированным хроническим риносинуситом у взрослых. (Приложение 1)

Ответственный за внедрение: докторант 3 года Сагандыкова К.Т.

Исполнители: докторант 3 года Сагандыкова К.Т.
к.м.н. доцент кафедры ЛОР-болезней Папулова Н.М.

Эффективность внедрения: предложенный нами алгоритм диагностики и лечения оптимизирует ведение пациентов с рефлюкс-ассоциированным хроническим риносинуситом.

Предложения, замечания, учреждения, осуществляющего внедрение: внедрить в перечень диагностики и лечения рефлюкс-ассоциированного хронического риносинусита.

Сроки внедрения: январь-февраль 2025г. данная методика в настоящее время используется в **ГКП на ПХВ «Городская поликлиника №11» акимата г. Астана, врачами общей практики и оториноларингологом**.

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ПРИЛОЖЕНИЕ Б

Свидетельства об авторском праве

ҚАЗАҚСТАН РЕСПУБЛИКАСЫ

РЕСПУБЛИКА КАЗАХСТАН

СВИДЕТЕЛЬСТВО

О ВНЕСЕНИИ СВЕДЕНИЙ В ГОСУДАРСТВЕННЫЙ РЕЕСТР ПРАВ НА ОБЪЕКТЫ, ОХРАНЯЕМЫЕ АВТОРСКИМ ПРАВОМ

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Дата создания объекта: 14.04.2025

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РЕСПУБЛИКА КАЗАХСТАН

СВИДЕТЕЛЬСТВО

О ВНЕСЕНИИ СВЕДЕНИЙ В ГОСУДАРСТВЕННЫЙ РЕЕСТР ПРАВ НА ОБЪЕКТЫ, ОХРАНЯЕМЫЕ АВТОРСКИМ ПРАВОМ

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СВИДЕТЕЛЬСТВО

О ВНЕСЕНИИ СВЕДЕНИЙ В ГОСУДАРСТВЕННЫЙ РЕЕСТР ПРАВ НА ОБЪЕКТЫ, ОХРАНЯЕМЫЕ АВТОРСКИМ ПРАВОМ

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Вид объекта авторского права: **произведение науки**

Название объекта: **Клинико-функциональная оценка влияния гастроэзофагеальной рефлюксной болезни на развитие и течение хронической патологии носа и носоглотки**

Дата создания объекта: **14.04.2025**

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Подписано ЭЦП С. Ахметов

ҚАЗАҚСТАН РЕСПУБЛИКАСЫ РЕСПУБЛИКА КАЗАХСТАН

СВИДЕТЕЛЬСТВО

О ВНЕСЕНИИ СВЕДЕНИЙ В ГОСУДАРСТВЕННЫЙ РЕЕСТР ПРАВ НА ОБЪЕКТЫ, ОХРАНЯЕМЫЕ АВТОРСКИМ ПРАВОМ

№ 57490 от «5» мая 2025 года

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Вид объекта авторского права: **произведение науки**

Название объекта: **Валидация оценочной шкалы Nasopharyngeal Reflux Endoscopic Score (NRES)рефлюкс-индуцированного хронического риносинусита**

Дата создания объекта: **30.04.2025**

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